SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Atenolol Sandoz 25, tabletten 25 mg
Atenolol Sandoz 50, tabletten 50 mg
Atenolol Sandoz 100, tabletten 100 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 25 mg atenolol.
Each tablet contains 50 mg atenolol.
Each tablet contains 100 mg atenolol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

25 mg tablets:
White, round biconvex tablets, on one side an inscription ‘25’ and` on the other side a score.
Diameter: 7 mm.

50 mg tablets:
White, round biconvex tablets, on one side an inscription ‘50’ and on the other side a score.
Diameter: 8 mm.

100 mg tablets:
White, round biconvex tablets, on one side an inscription ‘100’ and on the other side a score.
Diameter: 10 mm.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4.CLINICAL PARTICULARS

4.1 Therapeutic indications

- Hypertension
- Chronic stable angina pectoris
- Secondary prevention after acute myocardial infarction
- Supraventricular arrhythmias:
    - paroxysmal supraventricular tachycardia (in therapeutic or prophylactic treatment)
    - atrial fibrillation and atrial flutter: in case of inadequate response to maximum doses of cardiac glycosides; in cases where cardiac glycosides may be contra-indicated or may be associated with an unfavourable risk/benefit ratio.
- Ventricular arrhythmias:
    - ventricular extrasystoles (prophylactic or therapeutic treatment), if the extrasystoles are

the result of increased sympathetic activity
- ventricular tachycardias and ventricular fibrillation (prophylactic treatment), especially when the ventricular abnormality is the result of elevated sympathetic activity.

4.2 Posology and method of administration

Posology
The dose should be determined on an individual basis. It is recommended to start with the lowest possible dose so that heart failure, bradycardia and bronchial symptoms are noticed timely.
This is especially important in elderly. Further adaptation should be done gradually (e.g., once a week) under controlled conditions or based on the clinical effect.

Hypertension
A starting dose of 25 mg is recommended. The usual maintenance dose in hypertension is 50-100 mg daily. The maximum effect will be reached after 1-2 weeks. If further improvement of the blood pressure is desired, atenolol may be combined with another anti-hypertensive e.g., a diuretic.

Angina pectoris
50-100 mg daily depending on the clinical effect, in order to obtain a heartbeat in rest of 55-60 beats per minute (bpm). Increasing the dose above 100 mg daily does not generally lead to an increased anti-anginous effect. If desired the dose of 100 mg daily can be divided in two doses.

Arrhythmias
After controlling the arrhythmias with atenolol by intravenous use (when indicated) the recommended oral maintenance dose is of 50-100 mg daily.

Secondary prevention after myocardial infarction:
10 minutes after the discontinuation of the intravenous administration 50 mg, followed by another 50 mg 12 hours later, maintenance dose 100 mg daily in 1-2 doses for 6 days or until discharge from hospital.

Paediatric population
There is no experience with use of atenolol in children. It is therefore not recommended to use atenolol in children.

Elderly
In elderly therapy should be started with a lower dose. Dose should be titrated according to clinical effect.

Renal impairment

Glomerular filtration rate (ml/min/1.73 m^2 body surface	Recommended atenolol dose (mg/day)
> 35	No dose modification
15-35	25-50 (or 50-100 / 2 days)
< 15	25-50 / 2 days

In haemodialysis a 50 mg tablet is administered after each dialysis. The administration should be done in hospital since sudden decrease of the arterial pressure may occur.

Hepatic impairment
No dose modifications necessary.

Method of administration
The film-coated tablets should be swallowed whole with enough liquid before meals.
For the ease of swallowing the tablets can be broken in halves.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Cardiogenic shock
- Uncontrolled heart failure
- Sick sinus syndrome
- Second and third degree atrioventricular heart block
- Sinoatrial block
- Untreated pheochromocytoma
- Metabolic acidosis
- Bradycardia (< 45-50 bpm)
- Hypotension (systolic blood pressure less than 90 mmHg)
- Severe peripheral arterial circulatory disturbances
- Severe bronchial hyperresponsiveness (e.g., in severe bronchial asthma)
- Intravenous administration of calcium antagonists of the verapamil or diltiazem type or other antiarrhythmic substances (such as disopyramide) (except for intensive care medicine).

4.4 Special warnings and precautions for use

Ischaemic heart diseases
Especially in patients with ischaemic heart disease, treatment should not be discontinued suddenly. The dose should gradually be reduced, i.e. over 1-2 weeks, if necessary at the same time initiating replacement therapy, to prevent exacerbation of angina pectoris. In addition, hypertension and arrhythmias may develop. Furthermore, there is a risk on myocardial infarction and sudden death. Patients should be followed during withdrawal.

Untreated congestive heart disease
Although contraindicated in uncontrolled heart failure (see section 4.3), atenolol may be used in patients whose signs of heart failure have been controlled. Caution must be exercised in patients whose cardiac reserve is poor.

First degree heart block
Due to its negative effect on conduction time, atenolol should only be given with caution to patients with first-degree heart block.

Bradycardia
Atenolol may induce bradycardia. If the pulse rate decreases to less than 50-55 beats per minute at rest and the patient experiences symptoms related to the bradycardia, the dose should be reduced.

Prinzmetal's angina
Atenolol may increase the number and the duration of anginal attacks in patients with Prinzmetal's angina due to unopposed alpha-receptor mediated coronary artery vasoconstriction. For these patients atenolol should only be used with the utmost care.

Peripheral circulatory disorders
In patients with peripheral circulatory disorders (Raynaud's disease or syndrome, intermittent claudication), atenolol should be used with great caution as aggravation of these disorders may occur. Severe peripheral circulatory disorders are a contraindication (see section 4.3).

Respiratory disorders
In patients with chronic obstructive pulmonary disorders, airway obstructions may be aggravated. Therefore, atenolol should only be used for these patients with the utmost care. If increased airways resistance does occur, atenolol should be discontinued and bronchodilator therapy (e.g., salbutamol) administered if necessary.

Surgery
When it has been decided to interrupt a beta-blockade in preparation for surgery, therapy should be discontinued for at least 24 hours prior to the procedure. The risk-benefit assessment of stopping beta-blockade should be made for each patient. Continuation of beta-blockade reduces the risk of arrhythmias during induction and intubation, however the risk of hypotension may be increased as well. If treatment is continued, caution should be observed with the use of certain anaesthetic medicinal products. The patient may be protected against vagal reactions by intravenous administration of atropine.

Renal impairment
Since atenolol is excreted via the kidneys, dose should be reduced in patients with a creatinine clearance of below 35 ml/min/1.73 m^2 (see section 4.2). In very rare cases, worsening of renal function can occur during therapy with other beta-blockers. Renal function should be checked at regular intervals during therapy with atenolol.

Hepatic function
Because sever liver damage can occur during therapy with other beta-blockers, liver function should be checked at regular intervals during therapy with atenolol.

Lipid metabolism disorders
Therapy with atenolol can lead to disorders in lipid metabolism. A decrease in HDL cholesterol and an increase in plasma triglycerides have been observed.

Psoriasis
Patients with anamnestically known psoriasis should take atenolol only after careful consideration, as psoriasis may be aggravated.

Hypersensitivity reactions
Atenolol may increase both the sensitivity toward allergens and the seriousness of anaphylactic reactions and shock, especially when given to patients with a history of anaphylactic reaction. Beta-adrenergic blocking agents may impede the compensatory cardiovascular reactions associated with hypotension or shock. Atenolol may reduce the efficacy of adrenaline; such patients may be unresponsive to the usual doses of adrenaline used to treat the allergic reactions. Atenolol may cause a hypersensitivity reaction including angioedema and urticaria.

Diabetic patients
Treatment should be initiated with a glycaemia monitoring. Beta-blocking agents can mask the symptoms of hypoglycaemia, especially tachycardia, palpitations, sweating and tremor. Atenolol has no potentiating effect on insulin induced hypoglycaemia and the return to a normal glucose level is not altered. A careful medical supervision is necessary in patients with fluctuating blood sugar levels and in those with strict fasting and heavy physical exertion.

Thyrotoxicosis
Beta-blockade may mask cardiovascular signs of thyrotoxicosis.

Treated pheochromocytoma
In patients with pheochromocytoma atenolol must be administered only after alfa-receptor blockade. Blood pressure should be monitored closely.

Elderly
The elderly should be treated with caution, starting with a lower dose (see section 4.2).

[Nationally completed name] contains sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Calcium channel blockers
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.

Dihydropyridines
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
Digitalis glycosides, in association with beta-blockers, may increase atrioventricular conduction time. Concomitant administration may increase atrioventricular conduction time and bradycardia.

Clonidine
Beta-blockers may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two medicinal products 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. Concomitant administration may increase atrioventricular conduction time and bradycardia.

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

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

Iodinated contrast media
Atenolol may impede the compensatory cardiovascular reactions associated with hypotension or shock induced by iodinated contrast products. Beta-blockers, in general, have been associated with hypotension or shock induced by iodinated contrast products.

Insulin and oral antidiabetic medicinal products
Concomitant use with insulin and oral antidiabetic medicinal products may lead to the intensification of the blood sugar lowering effects of these medicinal products. Symptoms of hypoglycaemia, particularly tachycardia and tremor, may be masked or attenuated (see section 4.4).

Prostaglandin synthetase-inhibiting medicinal products

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

Anaesthetic agents, narcotics
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 medicinal products may result in attenuation of the reflex tachycardia and increase the risk of hypotension. Anaesthetic agents causing myocardial depression are best avoided.

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

Tricyclic antidepressants, barbiturates and phenothiazines as well as other antihypertensive agents
Concomitant administration may increase the blood pressure lowering effect.

Monoamine oxidase inhibitors
Simultaneous administration of atenolol with monoamine oxidase inhibitors (except for MAO-B inhibitors) is not recommended because it leads to an increased hypotensive effect of the beta blocker, however there is also an increased risk of a hypertensive crisis caused by the MAO inhibitor.

Sultopride
Atenolol should not be concomitantly administered with sultopride since there is an increased risk of ventricular arrhythmias, e.g., torsades de pointes.

Ampicillin
May reduce the bioavailability of atenolol. Therefore, the physician should watch for evidence of altered atenolol response especially when large doses of ampicillin are administered concomitantly.

Ophthalmic beta-blockers
Systemic effects of oral beta-blockers may be potentiated when used concomitantly with ophthalmic beta-blockers.

Peripheral muscle relaxants
Peripheral muscle relaxants (e.g., succinylcholine, tubocurarin) may reinforce and prolong the muscle-relaxing effect by atenolol.

Reserpine, alpha-methyldopa, guanfacine
Concomitant administration may may increase atrioventricular conduction time andbradycardia.

4.6 Fertility, pregnancy and lactation

Pregnancy
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.
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.
Advice: Neonates born to mothers who are receiving atenolol at parturition may be at risk of hypoglycaemia, bradycardia and respiratory depression (neonatal asphyxia). Therefore, atenolol should be discontinued 24-48 h before delivery. In case treatment was not discontinued during parturition the neonate needs to be monitored for above noted symptoms post parturition.

Breast-feeding
There is significant accumulation of atenolol in breast milk. Caution should be exercised when atenolol is administered to a woman who is breast-feeding. In case infants have been exposed to atenolol via breast-feeding monitoring for symptoms of hypoglycaemia, bradycardia and respiratory depression (neonatal asphyxia) is recommended.

Fertility
There are no data on the possible effects of atenonol on fertility.

4.7 Effects on ability to drive and use machines

Atenolol has no or negligible influence on the ability to drive and use machines. However, it should be taken into account that occasionally dizziness or fatigue may occur. Caution is recommended especially at the start of treatment, dose increase, and in interaction with alcohol.

4.8 Undesirable effects

The frequencies of adverse reactions 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

Immune system disorders
Very rare: serious allergic reactions that are not controlled by the usual adrenaline doses

Endocrine disorders
Uncommon: pre-diabetes mellitus, worsening of overt diabetes mellitus

Psychiatric disorders
Uncommon: sleep disturbances of type noted with other beta-blockers
Rare: mood changes, depression, nightmares, anxiety, confusion, psychoses and hallucinations

Nervous system disorders
Common: dizziness, sweating
Rare: headache, paraesthesia
Not known: central nervous system disorders, particularly at the start of treatment

Eye disorders
Uncommon: conjunctivitis
Rare: dry eyes, reduced lacrimation (to be considered when wearing contact lenses), visual impairment

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

Very rare: more intense anginal attacks-in patients with angina pectoris

Vascular disorders
Common: cold extremities
Rare: (Orthostatic) 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 disorders
Common: gastrointestinal problems (nausea, vomiting, diarrhoea and constipation)
Rare: dry mouth

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

Skin and subcutaneous tissue disorders
Rare: allergic skin reactions (redness, pruritus, rash), alopecia, psoriasiform skin reactions, exacerbation of psoriasis
Not known: hypersensitivity reactions, including angioedema and urticaria

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

Reproductive system and breast disorders
Rare: impotence, libido disorder

General disorders and administration site conditions
Common: fatigue

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

Reporting of 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 listed in Appendix V*.

4.9 Overdose

Symptoms
The symptoms of overdose may include hypotension, bradycardia leading to cardiac arrest, acute cardiac insufficiency, cardiogenic shock, bronchospasm, breathing difficulties, vomiting, impaired consciousness and generalized seizures.

Management
In the event of an overdose or a threatening drop in heart rate and/or blood pressure, the treatment with atenolol should be stopped. 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 medicinal products 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 inhaled bronchodilators or aminophylline IV. In case of generalized seizures, slow intravenous administration of diazepam is recommended. Atenolol is dialyzable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta-blocking agents, selective.
ATC code: C07AB03

Atenolol is a selective beta-1-adrenergic blocking agent, without intrinsic sympathomimetic of membrane stabilising characteristics. Clinical effects are reached fast and will maintain at least 24 hours after the intake of atenolol. Therefore both atenolol 50 and 100 mg tablets can be taken once daily, which simplifies the therapy. Atenolol is a very hydrophilic compound which passes the blood-brain barrier only in very limited amounts. This causes a relatively low incidence of central nervous system-adverse events. Atenolol mainly acts on the beta receptors of the heart and can therefore, contrary to non-selective beta-adrenergic blocking agents, be administered, under careful surveillance and check-up of the lung function, to patients with chronic obstructive pulmonal diseases, who cannot bear a non-selective beta-adrenergic blocking agent.
The beta-1-selectivity is reduced with increased dose. Beta-adrenergic blocking agents have a negative inotropic and chronotropic effect and inhibit the effect of catecholamines resulting in reduced heart rate and blood pressure.

5.2 Pharmacokinetic properties

The oral bioavailability is about 50 to 60%. The bioavailability is decreased by 20% when taken with food. Peak plasma concentrations are found 2-4 hours after repeated oral administration. There is a linear relationship between dose and plasma concentration. The inter-subject variability in AUC and C_{max} is about 30-40%. The volume of distribution is 50 to 75 L. The protein binding is less than 5%. Metabolism of atenolol is minimal. Most of an absorbed dose (85-100%) is excreted unchanged via the urine. The clearance is about 6 L/h and the half-life is about 6 to 9 hours. In elderly patients, clearance is decreased and elimination half-life increased. The clearance is correlated to renal function and the elimination is prolonged in patients with renal impairment. Impaired liver function does not influence the pharmacokinetics of atenolol.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety,

pharmacology, repeated dose toxicity, genotoxicity and carcinogenicity.

Reproduction studies show that atenolol has no teratogenic potential, however a study in rats showed that doses of 200 mg/kg/day on the 6th and 15th day of the pregnancy did result in a decrease in number of faetuses per dam and an increased incidence of embryo resorptions.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidon K 25
Maize starch
Microcrystalline cellulose
Sodium starch glycolate
Magnesium stearate
Colloidal anhydrous silica

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

Do not store above 25°C. Store in the original container in order to protect from moisture.

6.5 Nature and contents of container

The tablets are packed in Alu/PVC blisters and inserted in a carton.

Pack sizes:
25 mg tablets:
Blister: 28, 30, 56, 100, 100x1, 250 tablets

50 mg tablets:
Blister: 14, 20, 28, 30, 50, 56, 60, 98, 100, 100x1, 300, 500 tablets

100 mg tablets:
Blister: 14, 20, 21, 28, 30, 42, 50, 56, 60, 98, 100, 100x1, 300, 500 tablets

Not all pack sizes may be marketed.

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

Sandoz B.V.
Veluwezoom 22
1327 AH Almere

Nederland

8. MARKETING AUTHORISATION NUMBER

Atenolol Sandoz 25 is ingeschreven in het register onder RVG 24399
Atenolol Sandoz 50 is ingeschreven in het register onder RVG 14705
Atenolol Sandoz 100 is ingeschreven in het register onder RVG 14706

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning:
Atenolol Sandoz 25: 17 juli 2000
Atenolol Sandoz 50 en 100: 20 april 1990

Datum van laatste hernieuwing: 23 juni 2009

10. DATE OF REVISION OF THE TEXT

Laatste gedeeltelijke wijziging betreft rubrieken 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8 en 4.9: 7 maart 2021