SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Atenolol/Chloortalidon Sandoz 50/12,5, filmomhulde tabletten 50/12,5 mg
Atenolol/Chloortalidon Sandoz 100/25, filmomhulde tabletten 100/25 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 50 mg atenolol and 12.5 mg chlortalidone.

Each film-coated tablet contains 100 mg atenolol and 25 mg chlortalidone.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

50/12.5 mg film-coated tablets
White, round, film-coated tablets with the inscription A50 C12.5

100/25 mg film-coated tablets
White, round, film-coated tablets with the inscription A100 C25

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension that has not responded satisfactorily to treatment with a beta blocker or diuretic alone.

4.2 Posology and method of administration

One tablet daily. The clinical effect is achieved rapidly and lasts for at least 24 hours after administration of one single oral dose. [Nationally completed name] as fixed dosage combination is particularly utilized in maintenance therapy after the required dose has been established.

Use in the elderly
Dosage requirements are often lower in this age group.

Use in children and adolescents (< 18 years)

There is no experience with [nationally completed name] in children and adolescents. Therefore [nationally completed name] should not be administered to children and adolescents.

Use in patients with renal failure

Due to the properties of the chlorthalidone component, [nationally completed name] has reduced efficacy in the presence of renal insufficiency. This fixed dose combination should thus not be administrated to patients with severe renal impairment (see section 4.3).

Use in patients with hepatic failure
Dose adjustments are not required in patients with hepatic impairment.

4.3 Contraindications

[Nationally completed name] should not be used in patients with any of the following:
- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1
- Known hypersensitivity to sulphonamide derived medicinal products.
- second and third degree heart block
- bradycardia
- uncontrolled heart failure
- cardiogenic shock
- sick sinus syndrome
- untreated pheochromocytoma
- hypotension
- metabolic acidosis
- severe peripheral arterial circulatory disturbances
- severe renal failure
- Severe asthma or severe chronic obstructive pulmonary disease (see section 4.4).
- Pregnancy (see section 4.6)
- Lactation (see section 4.6)

4.4 Special warnings and precautions for use

Due to its beta-blocker component:

Although contra-indicated in uncontrolled heart failure (see section 4.3) [Nationally completed name] may be used in patients whose signs of heart failure have been controlled. Caution must be exercised in patients whose cardiac reserve is poor.

[Nationally completed name] 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 the use of [Nationally completed name] may be considered although utmost caution must be exercised.

Although contraindicated in severe peripheral arterial circulatory disturbances (see section 4.3) [Nationally completed name] may also aggravate less severe peripheral arterial circulatory disturbances.

Due to its negative effect on conduction time, caution must be exercised if it is given to patients with first degree heart block.

[Nationally completed name] may modify warning signs of hypoglycaemia as tachycardia, palpitation and sweating.

[Nationally completed name] may mask the cardiovascular signs of thyrotoxicosis.

[Nationally completed name] 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, the dose may be reduced.

[Nationally completed name] should not be discontinued abruptly in patients suffering from ischaemic heart disease.

[Nationally completed name] may cause a more severe reaction to a variety of allergens, when given to patients with a history of anaphylactic reaction to such allergens. Such patients may be unresponsive to the usual doses of adrenaline used to treat the allergic reactions.

Patients with bronchospastic disease should, in general, not receive beta-blockers due to increasing in airways resistance. Atenolol is a $beta_1$-selective beta-blocker, however this selectivity is not absolute. Therefore the lowest possible dose of [Nationally completed name] should be used and utmost caution must be exercised. If increased airways resistance does occur, [Nationally completed name] should be discontinued and bronchodilator therapy (e.g. salbutamol) administered if necessary.

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

In patients with pheochromocytoma [Nationally completed name] must be administered only after alfa-receptor blockade. Blood pressure should be monitored closely.

Caution must be exercised when using anaesthetic agents with [Nationally completed name]. The anesthetist 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.

Due to its chlorthalidone component:

Plasma electrolyte should be periodically determined in appropriate intervals to detect possible electrolyte imbalance especially hypokalaemia and hyponatraemia

Hypokalaemia and hyponatraemia may occur. Measurement of electrolytes is recommended, especially in the older patient, those receiving digitalis preparations for cardiac failure, those taking an abnormal (low in potassium) diet or those suffering from gastrointestinal complaints. Hypokalaemia may predispose to arrhythmias in patients receiving digitalis.

Because chlorthalidone may impair glucose tolerance diabetic patients should be aware of the potential for increased glucose levels. Close monitoring of glycaemia is recommended in the initial phase of therapy and in prolonged therapy test for glucosuria should be carried out at regular intervals.

In patients with impaired hepatic function or progressive liver disease, minor alterations in fluid and electrolyte balance may precipitate hepatic coma.

Hyperuricaemia may occur. Only a minor increase in serum uric acid usually occurs but in cases of prolonged elevation, the concurrent use of a uricosuric agent will reverse the hyperuricaemia.

Choroidal effusion, acute myopia and secondary angle-closure glaucoma

Sulphonamide or sulphonamide derivative medicinal product can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of medicinal product initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss.The primary treatment is to discontinue medicinal product intake as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulphonamide or penicillin allergy.

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

4.5 Interaction with other medicinal products and other forms of interaction

Due to atenolol:

Combined use of beta-blockers and calcium channel blockers with negative inotropic effects e.g, verapamil, diltiazem can lead to an exaggeration of these effects particularly in patients with impaired ventricular function and/or sino-atrial or atrio-ventricular 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.

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

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.

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

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

Due to chlorthalidone:

The chlorthalidone component may reduce the renal clearance of lithium leading to increased serum concentrations. Dose adjustments of lithium may therefore be necessary.

Due to the combination product:

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy:

[Nationally completed name] must not be given during pregnancy.
Lactation:
[Nationally completed name] must not be given during lactation.

4.7 Effects on ability to drive and use machines

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.

4.8 Undesirable effects

Very common:	≥1/10
Common:	≥1/100 to <1/10
Uncommon:	≥1/1000 to <1/100
Rare:	≥1/10 000 to <1/1000
Very rare:	<1/10 000,
not known:	(cannot be estimated from the available data)

The following side-effects may occur as a result of the atenolol component:

Blood and lymphatic system disorders
Rare: Purpura, thrombocytopenia,

Psychiatric disorders
Uncommon: Sleep disturbances of the type noted with other beta blockers
Rare: Mood changes, hallucinations, psychoses, confusion, nightmares

Nervous system disorders
Rare: Headaches, dizziness, paraesthesia

Eye disorders

Rare: Visual disturbances, dry eyes
Not known: Choroidal effusion, acute myopia and secondary angle-closure glaucoma

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 in patients with bronchial asthma or a history of asthmatic complaints.

Gastrointestinal disorders
Common: Gastro-intestinal disturbances
Rare: Dry mouth
Not known: Constipation

Hepatobiliary disorders
Rare: Hepatic toxicity including intrahepatic cholestasis.

Skin and subcutaneous tissue disorders
Rare: Alopecia, psoriasis like skin reactions, aggravation of psoriasis, skin rashes
Not known: Hypersensitivity reactions, including angioedema and urticaria.

Musculoskeletal and connective tissue disorders:

Not known: Lupus-like syndrome

Reproductive system and breast disorders
Rare: Impotence

General disorders and administration site conditions
Common: Fatigue

Investigations
Uncommon: Elevations of transaminase levels.
Very rare: An increase in A(nti) N(uclear) A(ntibodies) has been seen; its clinical relevance is not clear.

The following side-effects may occur as a result of the chlortalidone component:

Blood and lymphatic system disorders
Rare: Leucopenia

Gastrointestinal disorders
Common: Nausea

Hepatobiliary disorders
Rare: Pancreatitis

Investigations
Common: Hyperuricaemia, hyponatraemia, hypokalaemia, impaired glucose tolerance

Discontinuation of [Nationally completed name] should be considered if, according to clinical judgement, the well-being of the patient is adversely affected by any of the above reactions.

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

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 use 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 effects could 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.

Excessive diuresis should be countered by maintaining normal fluid and electrolyte balance.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: *Beta-blocking agents, selective and other diuretics*
ATC code: C07CB03

[Nationally completed name] combines the antihypertensive properties of the cardioselective beta blocker atenolol and the diuretic chlortalidone. Atenolol is a beta-1-selective adrenergic blocking agent without intrinsic sympathicomimetic or membrane stabilising properties. Atenolol is an extremely hydrophilic drug and passes the blood-brain barrier only to a very small extent. As a result, the incidence of CNS side-effects is relatively low. [Nationally completed name] is indicated for the treatment of patients in whom a beta blocker alone does not achieve a satisfactory effect and in whom the addition of a diuretic is considered desirable. Both active ingredients have long pharmacological half-lives so that an antihypertensive effect is guaranteed for at least 24 hours. In cases where the combination therapy is indicated, it simplifies the treatment and stimulates the patient compliance. The combination of a low dose of a beta blocker and a low dose of a diuretic, as in [Nationally completed name] 50/12.5, is particularly important for elderly patients in whom the usual doses of the ingredients are too high.

5.2 Pharmacokinetic properties

Combined administration of atenolol and chlortalidone has only a limited effect on the pharmocokinetic properties of the individual components.

Absorption and distribution
After oral administration approximately 50 % atenolol and approximately 60 % chlortalidone is absorbed.
The peak plasma concentrations of atenolol are observed 2 to 4 hours after repeated oral administration and of chlortalidone after approximately 12 hours. The latter varies considerably in between individuals. Atenolol has very hydrophylic properties. About 5% is bound to plasma proteins and atenolol passes the blood-brain barrier to a very limited extent. The rate of plasma protein binding of chlortalidone is approximately 75 %.
Both atenolol and chlortalidone pass the placenta and are excreted in mothers milk.

Biotransformation and elimination
Excretion of both substances predominantly occurs renal. After oral administration atenolol is excreted in urine for about 50%.
Atenolol is metabolised to a very limited extend. The elimination half-life is approximately 6-8 hours. The mean elimination half-life of chlortalidone is 50 hours. This is caused by the strong binding to red blood cells. After prolonged administration 30-60% of chlortalidone is excreted in urine unchanged. Elimination occurs to a limited extend by metabolism and hepatic excretion in the bile; no more than 10% is excreted in faeces.

5.3 Preclinical safety data

No particulars

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium carbonate
Maize starch
Gelatine
Sodium lauryl sulphate

Magnesium stearate
Hydroxypropylmethylcellulose
Macrogol 6000
Talc
Titanium dioxide (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Do not store above 25°C. Store in original packaging.

6.5 Nature and contents of container

The film-coated tablets are packed in PVC/Aluminium blisters and inserted in a carton.

Pack sizes:
14, 20, 28, 30, 50, 56 and 98 tablets (10 or 14 tablets per blister depending on the total pack size).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special precautions.

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

7. MARKETING AUTHORISATION HOLDER

Sandoz B.V.
Veluwezoom 22
Almere
Nederland

8. NUMMERS VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

Atenolol/Chloortalidon Sandoz is in het register ingeschreven onder:

RVG 15842, Atenolol/Chloortalidon Sandoz 50/12,5, tabletten 50 mg atenolol en 12,5 mg chloortalidon.
RVG 15843, Atenolol/Chloortalidon Sandoz 100/25, tabletten 100 mg atenolol en 25 mg chloortalidon.

9. DATUM VAN EERSTE VERLENING VAN DE VERGUNNING/HERNIEUWING VAN DE VERGUNNING

Datum van eerste verlening van de vergunning: 24 mei 1993.
Datum van laatste hernieuwing van de vergunning: 8 juni 2009.

10 DATUM VAN HERZIENING VAN DE TEKST

Laatste gedeeltelijke wijziging betreft de rubrieken 4.4 en 4.8; 9 maart 2021