# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

COMBISAR (Valsartan 160MG+Amlodipine besylate 5MG) film coated tablet

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

**Active Substances:**

Amlodipine besylate 6.94 mg (equivalent to 5 mg amlodipine)

Valsartan 160 mg

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film coated tablet

Yellowish-brown coloured, oblong, biconvex, one side is written '160' one side is written '5' film coated tablets.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

- Treatment of essential hypertension.
- It is indicated in adults whose blood pressure is not adequately controlled on amlodipine or valsartan monotherapy.

### 4.2 Posology and method of administration

Posology

Individual dose titration with the components (i.e. amlodipine and valsartan) is recommended before changing to the fixed dose combination. Fixed dose combination of COMBİSAR is considered in patients whose blood pressure is not adequately controlled with amlodipine 5 mg or valsartan 160 mg alone.

**Dosage / Frequency and duration of application:**

The recommended dose is one tablet per day (5 mg amlodipine and 160 mg valsartan or 10 mg amlodipine and 160 mg valsartan or 10 mg amlodipine and 320 mg valsartan). When clinically appropriate, direct change from monotherapy to the fixed-dose combination may be considered.

For convenience, patients receiving valsartan and amlodipine from separate tablets may be switched to COMBİSAR containing the same component doses.

The appropriate dose of COMBİSAR is recommended by the physician. The use of higher or lower doses may be advised according to the response to the treatment.

**Method of administration:**

Oral use.

COMBİSAR can be used with or without food.

It is recommended to take COMBİSAR with some water.

**Additional information on special populations:**

**Renal impairment:** No dosage adjustment is required for patients with mild to moderate renal impairment. Monitoring of potassium levels and creatinine is advised in moderate renal impairment. COMBİSAR is contraindicated in patients with severe renal impairment (see section 4.3).

**Hepatic impairment:** Caution should be exercised when administering COMBİSAR to patients with hepatic impairment or biliary obstructive disorders. In patients with mild to moderate hepatic impairment without cholestasis, the maximum recommended dose is 80 mg valsartan (see section 4.4). COMBİSAR is contraindicated in patients with severe hepatic impairment (see section 4.3).

**Pediatric population:**

The safety and efficacy of COMBİSAR in children aged below 18 years have not been established. No data are available.

**Geriatric population:**

Both components of the combination in elderly (65 years or above) or younger patients can be tolerated equally, the initial dose is not necessary in any dose adjustment.

## 4.3 Contraindications

- Hypersensitivity to the active substances, to dihydropyridine derivatives, or to any of the excipients
- Severe hepatic impairment, biliary cirrhosis or cholestasis.
- Severe renal impairment (glomerular filtration rate (GFR) <30 ml/min/1.73 m2) and patients undergoing dialysis

- Concomitant use of angiotensin receptor antagonists (ARB) - including valsartan - or of angiotensin converting enzyme (ACE) inhibitors with aliskiren in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m2) (see sections 4.4 and 4.5)
- Pregnancy (see sections 4.6).

## 4.4 Special warnings and precautions for use

Sodium and/or volume-depleted patients:

Excessive hypotension was seen in 0.4% of patients with uncomplicated hypertension treated with COMBİSAR in placebo-controlled studies. In patients with an activated renin-angiotensin system (such as volume- and/or salt-depleted patients receiving high doses of diuretics) who are receiving angiotensin receptor blockers, symptomatic hypotension may occur. Correction of this condition prior to administration of COMBİSAR or close medical supervision at the start of treatment is recommended.

If hypotension occurs with COMBİSAR, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. Treatment can be continued once blood pressure has been stabilised.

Hyperkalaemia:

Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other medicinal products that may increase potassium levels (heparin, etc.) should be undertaken with caution and with frequent monitoring of potassium levels.

Renal artery stenosis:

COMBİSAR should be used with caution to treat hypertension in patients with unilateral or bilateral renal artery stenosis or stenosis to a solitary kidney since blood urea and serum creatinine may increase in such patients.

Single or bilateral renal artery stenosis in patients with hypertension with ACE inhibitors in studies conducted in the levels of blood urea nitrogen and serum creatinine have been reported to increase. 12 patients with unilateral renal artery stenosis in clinical studies in the four-day valsartan in serum creatinine or blood urea nitrogen were observed a significant

increase in. Single or bilateral renal artery stenosis valsartan in patients with long term data are available to that seen with ACE inhibitors, a similar effect can be expected.

Renal impairment:
No dosage adjustment of COMBİSAR is required for patients with mild to moderate renal impairment (GFR >30 ml/min/1.73 m2). Monitoring of potassium levels and creatinine is advised in moderate renal impairment.

Renal transplantation:
Until now, there is no experience of the safety use of COMBİSAR in patients who have had a recent renal transplantation.

Hepatic impairment:
Valsartan is mostly eliminated unchanged via the bile. The half life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. Particular caution should be exercised when administering COMBİSAR to patients with mild to moderate hepatic impairment or biliary obstructive disorders.

In patients with mild to moderate hepatic impairment without cholestasis, the maximum recommended dose is 80 mg valsartan.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS):
In susceptible individuals, especially in the use of these systems will affect the combination of hypotension, syncope, stroke, hyperkalemia, and changes in renal function (including acute renal failure) have been reported. Because of the dual RAAS blockade led to the ARB or ACE inhibitors is not recommended for use with aliskiren. The concomitant use of ARBs - including valsartan - or of ACE inhibitors with aliskiren in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m2) is contraindicated (see sections 4.3).

Angioedema:

Angioedema, including swelling of the larynx and glottis, causing airway obstruction and/or swelling of the face, lips, pharynx and/or tongue, has been reported in patients treated with valsartan. Some of these patients previously experienced angioedema with other medicinal products, including ACE inhibitors. COMBİSAR should be discontinued immediately in patients who develop angioedema and should not be re-administered.

Primary hyperaldosteronism:
Patients with primary hyperaldosteronism should not be treated with the angiotensin II antagonist valsartan as their renin-angiotensin system is affected by the primary disease.

Heart failure/post-myocardial infarction:
As a consequence of the inhibition of the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotaemia and (rarely) with acute renal failure and/or death. Similar outcomes have been reported with valsartan. Evaluation of patients with heart failure or post-myocardial infarction should always include assessment of renal function.

In a long-term, placebo-controlled study (PRAISE) of amlodipine in patients with NYHA (New York Heart Association Classification) III and IV heart failure of non-ischaemic aetiology, amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.
Patients with acute myocardial infarction:
Especially in patients with severe obstructive coronary artery disease initiation or increase the dose of amlodipine worsening of angina and acute myocardial infarction following may develop.

Aortic and mitral valve stenosis:

As with all other vasodilators, special caution is indicated in patients suffering from mitral stenosis or significant aortic stenosis that is not high grade.

Valsartan / amlodipine non-patient population with hypertension, there has not been working on.

Laboratory findings:
Valsartan / amlodipine in hypertensive patients treated with a very small number compared to baseline significant changes were observed in laboratory tests. Placebo group (4.5%) compared amlodipine / valsartan (5.5%) and valsartan monotherapy (5.5%) slightly higher blood urea nitrogen groups respectively.

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

Interactions linked to amlodipine:
Caution required with concomitant use:

**CYP3A4 inhibitors:**

In elderly hypertensive patients in a daily dose of 180 mg diltiazem, amlodipine 5 mg amlodipine is administered simultaneously with 1.6-fold increase in systemic exposure was resulted. However, a strong CYP3A4 inhibitors (eg, ketoconazole, itraconazole, ritonavir, diltiazem, amlodipine plasma concentrations may increase to a higher dimension. Therefore, care must be taken when applying Amlodipine and CYP3A4 inhibitors simultaneously.

**CYP3A4 inducers (anticonvulsant agents [e. Carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone], rifampicin, Hypericum perforatum):**

There is no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use may give a lower plasma concentration of amlodipine. Amlodipine should be used with caution together with CYP3A4 inducers.

**Simvastatin:**

Co-administration of multiple doses of 10 mg amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. It is recommended to limit the dose of simvastatin to 20 mg daily in patients on amlodipine.

**To be taken into account with concomitant use:**

**Others:**

In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin, warfarin or ciclosporin.

**Interactions linked to valsartan:**

**Concomitant use not recommended:**

**Lithium:**

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors or angiotensin II receptor antagonists, including valsartan. Therefore, careful monitoring of serum lithium levels is recommended during concomitant use. If a diurectic is also used, the risk of lithium toxicity may presumably be increased further with COMBİSAR (see section 4.4.).

Potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels:

If a medicinal product that affects potassium levels is to be prescribed in combination with valsartan, monitoring of potassium plasma levels is advised.

**Interactions linked to aliskiren:**

The concomitant use of ARBs - including valsartan - or of ACE inhibitors with aliskiren is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m2) (see sections 4.3 and 4.4).

**Caution required with concomitant use:**

**Selective COX-2 inhibitors, acetylsalicylic acid (3 g / day), including non-steroidal antiinflammatory drugs (NSAIDs) and non-selective NSAIDs:**

When angiotensin II antagonists are administered simultaneously with NSAIDs attenuation of the antihypertensive effect may occur. Furthermore, concomitant use of angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function and an increase in serum potassium. Therefore, monitoring of renal function at the beginning of the treatment is recommended, as well as adequate hydration of the patient.

**Transporters:**

The results of an *in vitro* study with human liver tissue indicate that valsartan is a substrate of the hepatic uptake transporter OATP1B1 and of the hepatic efflux transporter MRP2. Co-administration of inhibitors of the uptake transporter (rifampicin, ciclosporin) or efflux transporter (ritonavir) may increase the systemic exposure to valsartan.

**Others:**

In monotherapy with valsartan, no interactions of clinical significance have been found with the following substances: cimetidine, warfarin, furosemide, digoxin, atenolol, indometacin, hydrochlorothiazide, amlodipine, glibenclamide.

**Common interactions with the combination:**

No drug interaction studies have been performed with COMBİSAR and other medicinal products.

**To be taken into account with concomitant use:**

**Other antihypertensive agents:**

Commonly used antihypertensive agents (e.g. alpha blockers, diuretics) and other medicinal products which may cause hypotensive adverse effects (e.g. tricyclic antidepressants, alpha blockers for treatment of benign prostate hyperplasia) may increase the antihypertensive effect of the combination.

**Additional information on special populations:**

There is no additional information on special population.

**Pediatric Population:** There is no clinical interaction study of pediatric use.

## 4.6 Fertility, pregnancy and lactation

**General advise**

Pregnancy Category is D.

**Women of childbearing potential / birth control (contraception)**

Before a planned pregnancy in women with childbearing potential, appropriate alternative therapy should be initiated.

**Pregnancy**

Directly acting on the RAAS, as with all medicines, COMBİSAR should not used during pregnancy (see section 4.3).
Amlodipine / valsartan are harmful pharmacological effects on pregnancy and / or the fetus / newborn.

Angiotensin II antagonists, depending on the mechanism of action, a risk on the fetus can not be ignored., it was reported that the use of valsartan as angiotensin converting enzyme (ACE) inhibitors (renin-angiotensin-aldosterone system (RAAS) acting on the specific drug class) In the second and third trimesters of pregnant women caused damage on developing fetus or death. In addition, in retrospective data, the use of ACE inhibitors during the first trimester of pregnancy, is associated with a potential risk of birth defects.
When pregnant women take valsartan accidentally, spontaneous abortion, oligohydramnios and neonatal renal dysfunction have been reported.

There is not enough clinical trial data about amlodipine in pregnant women. Animal studies with amlodipine, showed reproductive toxicity more than 8 times of the maximum recommended dose of 10 mg (see Section 5.3). Potential risk for humans is unknown.
If pregnancy is detected during treatment, stop taking COMBİSAR immediately.

**Lactation**
No information is available regarding the use of amplodipine or and valsartan during breast-feeding, therefore COMBİSAR is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

**Fertility**
There are not known effect on fertility.

### 4.7 Effects on ability to drive and use machines
Patients taking COMBİSAR and driving vehicles or using machines should take into account that dizziness or weariness may occasionally occur.

### 4.8 Undesirable effects
The safety of amplodipin/valsartan has been evaluated in five controlled clinical studies with 5,175 patients, 2,613 of whom received valsartan in combination with amlodipine.

Adverse reactions have been ranked under headings of frequency using 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).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

**Infections and infestations**

Common: Nasopharyngitis, Influenza.

**Immune system disorders**

Rare: Hypersensitivity.

**Psychiatric disorders**

Rare: Anxiety.

**Nervous system disorders**

Common: Headache.

Uncommon: Dizziness, somnolence, dizziness postural, paraesthesia.

**Eye disorders**

Rare: Visual disturbance.

**Ear and labyrinth disorders**

Uncommon: Vertigo.

Rare: Tinnitus.

**Cardiac disorders**

Uncommon: Tachycardia, palpitations.

Rare: Syncope.

**Vascular disorders**

Uncommon: Orthostatic hypotension.

Rare: Hypotension.

**Respiratory, thoracic and mediastinal disorders**

Uncommon: Cough, pharyngolaryngeal pain.

**Gastrointestinal disorders**

Uncommon: Diarrhoea, Nausea, abdominal discomfort, constipation, dry mouth.

**Skin and subcutaneous tissue disorders**

Uncommon: Erythema, Rash

Rare: Hyperhidrosis, Exanthema, Pruritus.

**Musculoskeletal and connective tissue disorders**

Uncommon: Joint swelling, back pain, arthralgia.

Rare: Muscle spasm, sensation of heaviness

**Renal and urinary disorders**

Rare: Pollakiuria, polyuria

**General disorders and administration site conditions**

Common: Oedema, pitting oedema, facial oedema, oedema peripheral, fatigue, flushing, asthenia, hot flush.

**Genito-urinary system disorders**

Rare: Erectyl disfunction.

Additional information on the combination:

Peripheral oedema, a recognised side effect of amlodipine, was generally observed at a lower incidence in patients who received the amlodipine/valsartan combination than in those who received amlodipine alone. In double-blind, controlled clinical trials, the incidence of peripheral oedema by dose was as follows:

| **% of patients who experienced peripheral oedema** | **Valsartan (mg)** | | | | |
|---|---|---|---|---|---|
| | **0** | **40** | **80** | **160** | 320 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Amlodipine (mg)** | **0** | 3.0 | 5.5 | 2.4 | 1.6 | 0.9 |
| | **2.5** | 8.0 | 2.3 | 5.4 | 2.4 | 3.9 |
| | **5** | 3.1 | 4.8 | 2.3 | 2.1 | 2.4 |
| | **10** | 10.3 | - | - | 9.0 | 9.5 |

The mean incidence of peripheral oedema evenly weighted across all doses was 5.1% with the amlodipine/valsartan combination.

In double-blind, active-controlled, or placebo-controlled completed clinical trials, peripheral edema incidence is statistically less in the combination-treated patients (5.8%) when compared with amlodipine treated patients (9%) as monotherapy.

Laboratory findings:
Significant changes were observed in laboratory tests of in small number hypertensive patients treated with Valsartan / amlodipine. When compared with Placebo group (4.5%) , incidence of increase of nitrogen in blood urea was slightly higher: amlodipine / valsartan (5.5%), alone valsartan (5.5%).

Additional information on the individual components:
Adverse reactions previously reported with one of the individual components (amlodipine or valsartan) may be potential adverse reactions with COMBİSAR as well, even if not observed in clinical trials or during the post-marketing period.

| | |
|---|---|
| Amlodipine *Common* | Somnolence, dizziness, palpitations, abdominal pain, nausea, ankle swelling. |
| *Uncommon* | Insomnia, mood changes (including anxiety), depression, tremor, dysgeusia, syncope, hypoesthesia, visual disturbance (including diplopia), tinnitus, hypotension, dyspnoea, rhinitis, vomiting, dyspepsia, alopecia, purpura, skin discolouration, hyperhidrosis, pruritus, exanthema, myalgia, muscle cramps, pain, micturition disorder, increased urinary frequency, impotence, |

| | |
|---|---|
| | gynaecomastia, chest pain, malaise, weight increase, weight decrease. |
| *Rare* | Confusion. |
| *Very rare* | Leukocytopenia, thrombocytopenia, allergic reactions, hyperglycaemia, hypertonia, peripheral neuropathy, myocardial infarction, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation), vasculitis, pancreatitis, gastritis, gingival hyperplasia, hepatitis, jaundice, hepatic enzymes increased*, angioedema, erythema multiforme, urticaria, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke oedema, photosensitivity. |

* mostly consistent with cholestasis

Exceptional cases of extrapyramidal syndrome have been reported.

| | |
|---|---|
| Valsartan: | |
| Not known | Decrease in haemoglobin, decrease in haematocrit, neutropenia, thrombocytopenia, increase of serum potassium, elevation of liver function values including increase of serum bilirubin, renal failure and impairment, elevation of serum creatinine, angioedema, myalgia, vasculitis, hypersensitivity including serum sickness. |

**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 EFDA

yellow Card Scheme, online at https://primaryreporting.who-umc.org/ET or toll free call 8482 to Ethiopian food and drug authority (EFDA).

### 4.9 Overdose

There is no experience of overdose with Amlodipine / valsartan. Major symptom of overdose with valsartan probably is pronounced hypotension with dizziness .

Overdose with amlodipine excessive peripheral vasodilatation and possibly reflex tachycardia may result. Up to and including shock with fatal outcome. Marked and potentially prolonged systemic hypotension up to and including shock with fatal outcome have been reported.
Clinically significant hypotension due to Exforge overdose calls for active cardiovascular support, including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output.
A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use.

If the ingestion is recent, induction of vomiting or gastric lavage may be considered. Administration of activated charcoal to healthy volunteers immediately or up to two hours after ingestion of amlodipine has been shown to significantly decrease amlodipine absorption.

Intravenous calcium gluconate, calcium channel blocker, can help in the reverse effects.

Both valsartan and amlodipine are unlikely to be removed by hemodialysis.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system; angiotensin II antagonists (valsartan), combinations; dihydropyridin derivates (amplodipine)
ATC code: C09DB01
COMBİSAR combines two antihypertensive compounds with complementary mechanisms to control blood pressure in patients with essential hypertension: amlodipine belongs to the calcium antagonist class and valsartan to the angiotensin II antagonist class of medicines. The combination of these substances has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.
**Amlodipine:**

The amlodipine component of COMBİSAR inhibits the transmembrane entry of calcium ions into cardiac and vascular smooth muscle. The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle, causing reductions in peripheral vascular resistance and in blood pressure. Experimental data suggest that amlodipine binds to both dihydropyridine and non-dihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels.

Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation, resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing.
Plasma concentrations correlate with effect in both young and elderly patients.

In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow, without change in filtration fraction or proteinuria.

As with other calcium channel blockers, haemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In haemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and humans, even when co-administered with beta blockers to humans.

Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or humans. In clinical studies in which amlodipine was administered in combination with beta blockers to patients with either hypertension or angina, no adverse effects on electrocardiographic parameters were observed.

Amlodipine chronic stable angina, vasospastic angina and angiographically documented coronary artery disease who are proven to have beneficial effects.

**Valsartan:**

Valsartan is an orally active, potent and specific angiotensin II receptor antagonist. It acts selectively on the receptor subtype AT1, which is responsible for the known actions of angiotensin II. The increased plasma levels of angiotensin II following AT1 receptor blockade with valsartan may stimulate the unblocked receptor subtype AT2, which appears to counterbalance the effect of the AT1 receptor. Valsartan does not exhibit any partial agonist activity at the AT1 receptor and has much (about 20,000-fold) greater affinity for the AT1 receptor than for the AT2 receptor.

Valsartan does not inhibit ACE, also known as kininase II, which converts angiotensin I to angiotensin II and degrades bradykinin. Since there is no effect on ACE and no potentiation of bradykinin or substance P, angiotensin II antagonists are unlikely to be associated with coughing. In clinical trials where valsartan was compared with an ACE inhibitor, the incidence of dry cough was significantly ($p < 0.05$) lower in patients treated with valsartan than in those treated with an ACE inhibitor (2.6% versus 7.9%, respectively). In a clinical trial of patients with a history of dry cough during ACE inhibitor therapy, 19.5% of trial subjects receiving valsartan and 19.0% of those receiving a thiazide diuretic experienced coughing, compared to 68.5% of those treated with an ACE inhibitor ($p < 0.05$). Valsartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Administration of valsartan to patients with hypertension results in a drop in blood pressure without affecting pulse rate.

In most patients, after administration of a single oral dose, onset of antihypertensive activity occurs within 2 hours, and the peak drop in blood pressure is achieved within 4–6 hours. The antihypertensive effect persists over 24 hours after administration. During repeated administration, the maximum reduction in blood pressure with any dose is generally attained within 2–4 weeks and is sustained during long-term therapy. Abrupt withdrawal of valsartan has not been associated with rebound hypertension or other adverse clinical events.

Valsartan significantly decreased the rate of hospitalization in patients with chronic heart failure (NYHA class II-IV). The benefits were observed much more in patients who are not receiving ACE inhibitor or a beta-blocker. Valsartan also reduced cardiovascular mortality in clinically stable patients with left ventricular dysfunction or with left ventricular failure.

**Amlodipin/Valsartan:**

Over 1,400 hypertensive patients received COMBİSAR once daily in two placebo-controlled trials. The antihypertensive effect of a single dose of the combination persisted for 24 hours.

Adults with mild to moderate uncomplicated essential hypertension (mean sitting diastolic blood pressure ≥95 and <110 mmHg) were enrolled. Patients with high cardiovascular risks – heart failure, type I and poorly controlled type II diabetes and history of myocardial infarction or stroke within one year – were excluded.

The combination of amlodipine and valsartan produces dose-related additive reduction in blood pressure across its therapeutic dose range. The antihypertensive effect of a single dose of the combination persisted for 24 hours.

Amlodipine / valsartan (amlodipine besilate / valsartan), diastolic blood pressure ≥ 95 mmHg and <110 mmHg in hypertensive patients was studied in 2 placebo-controlled studies. In the first study (baseline blood pressure 153/99 mmHg), 5/80 mg, 5/160 mg, and 5/320 mg dose of amlodipine / valsartan blood pressure 20-23/14-16 mmHg lowering with placebo decline 7/7 mmHg has been . In the second study (baseline blood pressure 157/99 mmHg), 10/160 mg, and 10/320 mg dose of amlodipine / valsartan, the blood pressure lowering with placebo mmHg decrease 28/18-19 13/9 mmHg has been.

A multicentre, randomised, double-blind, active-controlled, parallel-group trial showed normalisation of blood pressure (trough sitting diastolic blood pressure <90 mmHg at the end of the trial) in patients not adequately controlled on valsartan 160 mg in 75% of patients treated with amlodipine/valsartan 10 mg/160 mg and 62% of patients treated with amlodipine/valsartan 5 mg/160 mg, compared to 53% of patients remaining on valsartan 160 mg. The addition of amlodipine 10 mg and 5 mg produced an additional reduction in systolic/diastolic blood pressure of 6.0/4.8 mmHg and 3.9/2.9 mmHg, respectively, compared to patients who remained on valsartan 160 mg only.

A multicentre, randomised, double-blind, active-controlled, parallel-group trial showed normalisation of blood pressure (trough sitting diastolic blood pressure <90 mmHg at the end of the trial) in patients not adequately controlled on amlodipine 10 mg in 78% of patients treated with amlodipine/valsartan 10 mg/160 mg, compared to 67% of patients remaining on amlodipine 10 mg. The addition of valsartan 160 mg produced an additional reduction in

systolic/diastolic blood pressure of 2.9/2.1 mmHg compared to patients who remained on amlodipine 10 mg only.

COMBİSAR was also studied in an active-controlled study of 130 hypertensive patients with mean sitting diastolic blood pressure ≥110 mmHg and <120 mmHg. In this study (baseline blood pressure 171/113 mmHg), an COMBİSAR regimen of 5 mg/160 mg titrated to 10 mg/160 mg reduced sitting blood pressure by 36/29 mmHg as compared to 32/28 mmHg with a regimen of lisinopril/hydrochlorothiazide 10 mg/12.5 mg titrated to 20 mg/12.5 mg.

In two long-term follow-up studies the effect of COMBİSAR was maintained for over one year. Abrupt withdrawal of Amplodipine/Valsartan has not been associated with a rapid increase in blood pressure.

Blood pressure is adequately controlled with amlodipine but unacceptable levels in patients with edema, combination therapy similar blood pressure control with less edema can provide.

Amplodipine/Valsartan has not been studied in any patient population other than hypertension. Valsartan has been studied in patients with post myocardial infarction and heart failure. Amlodipine has been studied in patients with chronic stable angina, vasospastic angina and angiographically documented coronary artery disease.

## 5.2 Pharmacokinetic properties

**General Properties**

After administration of COMBİSAR orally, peak plasma concentrations of valsartan and amlodipine are reached in 3 and 6-8 hours respectively. The rate and extent of absorption of

COMBİSAR are equivalent to the bioavailability of valsartan and amlodipine when administered as individual tablets.

Amlodipine

Absorption:

After oral administration of therapeutic doses of amlodipine alone, peak plasma concentrations of amlodipine are reached in 6–12 hours. Absolute bioavailability has been calculated as between 64% and 80%. Amlodipine bioavailability is unaffected by food ingestion.

Distribution:

Volume of distribution is approximately 21 l/kg. *In vitro* studies with amlodipine have shown that approximately 97.5% of circulating drug is bound to plasma proteins.

Biotransformation:

Amlodipine is extensively (approximately 90%) metabolised in the liver to inactive metabolites.

Elimination:

Amlodipine elimination from plasma is biphasic, with a terminal elimination half-life of approximately 30 to 50 hours. Steady-state plasma levels are reached after continuous administration for 7–8 days. Ten per cent of original amlodipine and 60% of amlodipine metabolites are excreted in urine.

Linearity- non-linearity:

Amlodipine exhibit linear pharmacokinetics.

Valsartan

Absorption:

Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2–4 hours. Mean absolute bioavailability is 23%. Food decreases exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (Cmax) by about 50%, although from about 8 h post dosing plasma valsartan concentrations are similar for the fed and fasted groups. This reduction in AUC is not, however, accompanied by a clinically significant reduction in the therapeutic effect, and valsartan can therefore be given either with or without food.

Distribution:

The steady-state volume of distribution of valsartan after intravenous administration is about 17 litres, indicating that valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (94–97%), mainly serum albumin.

Biotransformation:

Valsartan is not transformed to a high extent as only about 20% of dose is recovered as metabolites. A hydroxy metabolite has been identified in plasma at low concentrations (less than 10% of the valsartan AUC). This metabolite is pharmacologically inactive.

Elimination:

Valsartan shows multiexponential decay kinetics (t½α <1 h and t½ß about 9 h). Valsartan is primarily eliminated in faeces (about 83% of dose) and urine (about 13% of dose), mainly as unchanged drug. Following intravenous administration, plasma clearance of valsartan is about 2 l/h and its renal clearance is 0.62 l/h (about 30% of total clearance). The half-life of valsartan is 6 hours.

Linearity- non-linearity:

Valsartan exhibit linear pharmacokinetics.

**Special Populations**

Renal impairment:

The pharmacokinetics of amlodipine, is not significantly influenced by renal impairment. In patients with renal insufficiency at different levels, no correlation was seen between renal function (creatinine clearance) and systemic exposure to valsartan (AUC). Therefore, patients with mild to moderate renal impairment may receive the usual initial dose (see section 4.2. and 4.4.).

Hepatic impairment:

Patients with hepatic impairment have decreased clearance of amlodipine with resulting increase of approximately 40–60% in AUC. On average, in patients with mild to moderate chronic liver disease exposure (measured by AUC values) to valsartan is twice that found in healthy volunteers (matched by age, sex and weight). Caution should be exercised in patients with liver disease (see section 4.2 and 4.4).

Pediatric population:

No pharmacokinetic data are available in the pediatric population.

Elderly

Time to peak plasma amlodipine concentrations is similar in young and elderly patients. In elderly patients, amlodipine clearance tends to decline, causing increases in the area under the curve (AUC) and elimination half-life.

Compared with the young, systemic exposure to valsartan is slightly higher, but its clinical significance is not shown. These two components work equally well in young and elderly patients tolerated the usual dosing regimen is recommended (see section 4.2.). Caution should be exercised in dose escalation.

Age, gender and race:
Age, gender and race do not influence the response to COMBİSAR.

## 5.3 Preclinical safety data

Amlodipine/Valsartan
Adverse reactions observed in animal studies with possible clinical relevance were as follows:

Histopathological signs of inflammation of the glandular stomach was seen in male rats at an exposure of about 1.9 (valsartan) and 2.6 (amlodipine) times the clinical doses of 160 mg valsartan and 10 mg amlodipine. At higher exposures, there were ulceration and erosion of the stomach mucosa in both females and males. Similar changes were also seen in the valsartan alone group (exposure 8.5–11.0 times the clinical dose of 160 mg valsartan).

An increased incidence and severity of renal tubular basophilia/hyalinisation, dilation and casts, as well as interstitial lymphocyte inflammation and arteriolar medial hypertrophy were found at an exposure of 8–13 (valsartan) and 7–8 (amlodipine) times the clinical doses of 160 mg valsartan and 10 mg amlodipine. Similar changes were found in the valsartan alone group (exposure 8.5–11.0 times the clinical dose of 160 mg valsartan).

In an embryo-foetal development study in the rat, increased incidences of dilated ureters, malformed sternebrae, and unossified forepaw phalanges were noticed at exposures of about 12 (valsartan) and 10 (amlodipine) times the clinical doses of 160 mg valsartan and 10 mg amlodipine. Dilated ureters were also found in the valsartan alone group (exposure 12 times the clinical dose of 160 mg valsartan). There were only modest signs of maternal toxicity (moderate reduction of body weight) in this study. The no-observed-effect-level for developmental effects was observed at 3- (valsartan) and 4- (amlodipine) fold the clinical exposure (based on AUC).

For the single compounds there was no evidence of mutagenicity, clastogenicity orB carcinogenicity.

Amlodipine:

For amlodipine other than clinical and clinical safety data are well known. Carcinogenicity studies, mutagenicity studies related findings were observed.

10 mg / kg / day ( 50-kg patient weight , based on mg/m2 in terms of 10 mg maximum recommended human dose of 8 times ) up to doses of amlodipine -treated rat fertility on any effects were observed ( mating previous 64 days men for 14 days and females ) . Pregnant rats and rabbits, during the major period of organogenesis about 10 mg of amlodipine / kg / day by oral route up to doses of amlodipine maleate when treated with teratogenicity or embryo / fetal toxicity was detected proof. However, birth size was significantly reduced (approximately 50% ) and intrauterine death toll was significantly increased ( about 5 times ). At this dose of amlodipine and gestational period in rats and has been shown to extend the delivery time .

Amlodipine mutagenicity, klastojenisit, reproductive performance and individually tested for carcinogenicity and negative findings were obtained.

Valsartan:

Valsartan mutagenicity , klastojenisit , reproductive performance and individually tested for carcinogenicity and negative findings were obtained.

Carried out in a number of various animal species in preclinical safety studies in humans to prevent the use of therapeutic doses of valsartan findings were not found. Preclinical safety studies, high valsartan doses (200 to 600 mg / kg body weight) in rats erythrocyte parameters decrease (erythrocytes, hemoglobin, hematocrit), and renal hemodynamic changes to the argument (in males it slightly increased plasma urea and renal tubular hyperplasia and basophilia) led . These doses in rats (200 and 600 mg / kg / day) based on mg/m2 of the maximum recommended human dose of about 6 to 18 times (in account 320 mg / day and 60 kg patient assumes an oral dose). Marmosets at similar doses , the changes are similar, but increased urea and creatinine, especially one that contains the changes seen in the direction of development of nephropathy is more severe in the kidney . In both species was also observed in renal juxtaglomerular cells hypertrophy . All changes valsartan in particular prolonged hypotension marmoset pharmacological effect is presumed to result . Juxtaglomerular cells in humans at therapeutic doses of valsartan hypertrophy is not considered to have an interest . Mice , rats and rabbits with embryo-fetal development studies ( Part II ) in rats ≥ 200 mg / kg

/ day of valsartan in doses in rabbits ≥ 10 mg / kg / day doses of maternal toxicity associated with foetotoxicity was observed . Peri and postnatal developmental toxicity (Section III) study, the last trimester and during lactation 600 mg / kg offspring of rats given a slightly reduced survival rate and showed some developmental delay.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Pregelatinized Starch
colloidal silicon dioxide
Microcrystalline cellulose
Crospovidone Type A
magnesium stearate
Hydroxypropyl methyl cellulose
polyethylene glycol
Talc
titanium dioxide
red iron oxide
yellow iron oxide

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

24 months

### 6.4 Special precautions for storage

Store below 30°C at room temperature.
Store in the original package to protect from humidity.

### 6.5 Nature and contents of container <and special equipment for use, administration or implantation>

28 film coated tablets are packed in Al/Al foil blister in the cartoon box with patient information leaflet.

### 6.6 Special precautions for disposal <and other handling>

No special requirements.

Unused product or waste materials should be disposed of in accordance with "Medical Waste Control Regulation" and "Packaging and Packaging Waste Control Regulation".

## 7. MARKETING AUTHORISATION HOLDER

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## 8. MARKETING AUTHORISATION NUMBER(S)

**Certificate No: 05802/07776/REN/2021**

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Mar 23, 2021

## 10. DATE OF REVISION OF THE TEXT

September 2023