



1. NAME OF THE MEDICINAL PRODUCT

DIOVAN® 40 mg film-coated tablets
DIOVAN® 80 mg film-coated tablets
DIOVAN® 160 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 40 mg of valsartan.
Each film-coated tablet contains 80 mg of valsartan.
Each film-coated tablet contains 160 mg of valsartan.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Diovan® 40 mg Film-coated tablet: Yellow, ovaloid film-coated tablet with bevelled edges, slightly convex, scored on one side; with debossing "D" on one side of the score and "O" on the other side of the score and "NVR" on the reverse side of the tablet. The tablet can be divided into equal doses.

Diovan® 80 mg Film-coated tablet: Pale red, round film-coated tablet with bevelled edges, scored on one side with debossing "D" on one side of the score and "V" on the other side of the score and "NVR" on the reverse side of the tablet.

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

Diovan® 160 mg Film-coated tablet: Grey-orange, ovaloid film-coated tablet slightly convex, one side with debossing "DX" and "NVR" on the reverse side of the tablet.

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

There is no information regarding chewing or crushing of the tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension (Diovan 80 mg and 160 mg)

For treatment of hypertension.

Heart failure (Diovan 40 mg, 80 mg and 160 mg)

Diovan is indicated for the treatment of heart failure (NYHA class II-IV) in patients who are intolerant of angiotensin converting enzyme inhibitors. In a controlled clinical trial, Diovan significantly reduced hospitalizations for heart failure. There is no evidence that Diovan provides added benefits when it is used with an adequate dose of an ACE inhibitor.

Myocardial infarction (Diovan 40 mg, 80 mg and 160 mg)

Diovan is indicated to improve survival following myocardial infarction in clinically stable patients with signs symptoms or radiological evidence of left ventricular failure and/or with left ventricular systolic dysfunction.

4.2 Posology and method of administration

Hypertension (only 80mg and 160 mg)

The recommended dose of Diovan is 80 mg once daily for most patients. The antihypertensive effect is substantially present within 2 weeks and maximal effects are seen after 4 weeks. In some patients whose blood pressure is not adequately controlled, the dose may be increased to 160 mg, or a greater decrease in BP may be achieved by adding in a thiazide diuretic.

Diovan may also be administered with other antihypertensive agents (see section 4.3, 4.4, 4.5 and 5.1).

Diovan is not indicated for children and adolescents under 18 years old.

Heart failure (40 mg, 80 mg and 160 mg)

The recommended starting dose of Diovan is 40 mg twice daily. Uptitration to 80 mg and 160 mg twice daily should be done to the highest dose, as tolerated by the patient. Consideration should be given to reducing the dose of concomitant diuretics. The maximum daily dose administered in clinical trials is 320 mg in divided doses.

Post-myocardial infarction (40 mg, 80 mg and 160 mg)

Therapy may be initiated as early as 12 hours after a myocardial infarction. After an initial dose of 20 mg twice daily, valsartan therapy should be titrated to 40 mg, 80 mg, and 160 mg twice daily over the next few weeks. The starting dose is provided by the 40 mg divisible tablet.

Achievement of the target dose of 160 mg twice daily should be based on the patient's tolerability to valsartan during titration. If symptomatic hypotension or renal dysfunction occurs, consideration should be given to a dose reduction.

Valsartan may be used in patients treated with other post-myocardial infarction therapies, e.g. thrombolytics, acetylsalicylic acid, beta blockers, statins.

Additional information on special populations

Use in patients over 75 years:

A lower starting dose of 40 mg once daily is recommended.

Use in patients with renal impairment:

Hypertension- No initial dose adjustment is required in patients with mild renal impairment (i.e. creatinine clearance 20-50 ml/min). For patients with moderate to severe renal impairment or patients on dialysis, a lower starting dose of 40 mg once daily is recommended.

Heart Failure- Evaluation of patients with heart failure should always include assessment of renal function.

Post myocardial infarction- In the indication of current myocardial infarction no dosage adjustment is required for patients with mild renal impairment. There are currently no data available in post myocardial patients with severe renal impairment (serum creatinine $\geq 221 \mu\text{mol/l}$). Diovan should therefore be used with caution in such patients, with appropriate assessment of renal function (see Section 4.4)

Concomitant use of Diovan with Aliskiren is contraindicated in patients with renal impairment (GFR $< 60 \text{ ml/min/1.73 m}^2$) (see section 4.3).

Patients with Hepatic impairment

Hypertension

Use in patients with mild to moderate hepatic impairment:

Treatment should commence at dose of 40 mg once daily. A daily dose of 80mg valsartan should not be exceeded. Patients with severe hepatic impairment, cirrhosis or biliary obstruction should not use Diovan (see Section 4.3 Contraindications).

Post-myocardial infarction

Use in patients with mild to moderate hepatic impairment:

Doses higher than 80mg twice daily should only be considered if the clinical benefit is likely to outweigh the possible risk associated with increased exposure of valsartan. Patients with severe hepatic impairment, cirrhosis or biliary obstruction should not use Diovan (see Section 4.3 Contraindications).

Use in patients with intravascular volume depletion:

For those patients who have intravascular volume depletion (e.g. those treated with high dose diuretics who are unable to have their dose of diuretic reduced) a starting dose of 40 mg is recommended.

Paediatric population:

Diovan is not recommended for the treatment of heart failure or recent myocardial infarction in children and adolescents below the age of 18 years due to the lack of data on safety and efficacy.

Diovan is not indicated for children and adolescents under 18 years old.

Diovan must not be used in combination with Aliskiren in patients with diabetes mellitus (see section 4.3)

Method of administration

Diovan may be taken independently of a meal and should be administered with water.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Severe hepatic impairment, biliary cirrhosis, and cholestasis.
- Second and third trimester of pregnancy (see sections 4.4 and 4.6).
- Concomitant use of Diovan with aliskiren-containing products in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m²) (see sections 4.5 and 5.1).

4.4 Special warnings and precautions for use

Hyperkalaemia

Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other agents that may increase potassium levels (heparin, etc.) is not recommended. Monitoring of potassium should be undertaken as appropriate.

Impaired renal function

There is currently no experience on the safe use in patients with a creatinine clearance <10 ml/min and patients undergoing dialysis, therefore valsartan should be used with caution in these patients. No dose adjustment is required for adult patients with creatinine clearance >10 ml/min (see sections 4.2 and 5.2).

Hepatic impairment

In patients with mild to moderate hepatic impairment without cholestasis, Diovan should be used with caution (see sections 4.2 and 5.2).

Sodium- and/or volume-depleted patients

In severely sodium-depleted and/or volume-depleted patients, such as those receiving high doses of diuretics, symptomatic hypotension may occur in rare cases after initiation of therapy with Diovan. Sodium and/or volume depletion should be corrected before starting treatment with Diovan, for example by reducing the diuretic dose.

Renal artery stenosis

In patients with bilateral renal artery stenosis or stenosis to a solitary kidney, the safe use of Diovan has not been established.

Short-term administration of Diovan to twelve patients with renovascular hypertension secondary to unilateral renal artery stenosis did not induce any significant changes in renal haemodynamics, serum creatinine, or blood urea nitrogen (BUN). However, other agents that affect the renin-angiotensin system may increase blood urea and serum creatinine in patients with unilateral renal artery stenosis, therefore monitoring of renal function is recommended when patients are treated with valsartan.

Kidney transplantation

There is currently no experience on the safe use of Diovan in patients who have recently undergone kidney transplantation.

Primary hyperaldosteronism

Patients with primary hyperaldosteronism should not be treated with Diovan as their renin-angiotensin system is not activated.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy

As with all other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or hypertrophic obstructive cardiomyopathy (HOCM).

Pregnancy

Angiotensin II Receptor Antagonists (AIIAs) should not be initiated during pregnancy. Unless continued AIIAs therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIAs should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Recent-myocardial infarction (40 mg, 80 mg and 160 mg)

The combination of captopril and valsartan has shown no additional clinical benefit, instead the risk for adverse events increased compared to treatment with the respective therapies (see sections 4.2 and 5.1). Therefore, the combination of valsartan with an ACE inhibitor is not recommended.

Caution should be observed when initiating therapy in post-myocardial infarction patients. Evaluation of post-myocardial infarction patients should always include assessment of renal function (see section 4.2).

Use of Diovan in post-myocardial infarction patients commonly results in some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension is not usually necessary provided dosing instructions are followed (see section 4.2).

Heart Failure (40 mg, 80 mg and 160 mg)

The risk of adverse reactions, especially hypotension, hyperkalaemia and decreased renal function (including acute renal failure), may increase when Diovan is used in combination with an ACE inhibitor. In patients with heart failure, the triple combination of an ACE inhibitor, a beta blocker and Diovan has not shown any clinical benefit (see section 5.1). This combination apparently increases the risk for adverse events and is therefore not recommended. Triple combination of an ACE inhibitor, a mineralocorticoid receptor antagonist and valsartan is also not recommended. Use of these combinations should be under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

Caution should be observed when initiating therapy in patients with heart failure. Evaluation of patients with heart failure should always include assessment of renal function (see section 4.2).

Use of Diovan in patients with heart failure commonly results in some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension is not usually necessary provided dosing instructions are followed (see section 4.2).

In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure), treatment with ACE inhibitors has been associated with oliguria and/or progressive azotaemia and in rare cases with acute renal failure and/or death. As valsartan is an angiotensin II receptor blocker, it cannot be excluded that the use of Diovan may be associated with impairment of the renal function.

ACE inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

History of 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 drugs including ACE inhibitors. Diovan should be immediately discontinued in patients who develop angioedema, and Diovan should not be re-administered (see section 4.8).

Dual Blockade of the Renin-Angiotensin-Aldosterone System (RAAS)

There is evidence that the concomitant use of ACE inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia, and decreased renal function (including acute renal failure). Dual blockade of the RAAS through the combined use of ACE inhibitors, angiotensin II receptor blockers or Aliskiren is therefore not recommended (see sections 4.5 and 5.1).

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Paediatric population

Impaired renal function

Use in paediatric patients with a creatinine clearance <30 ml/min and paediatric patients undergoing dialysis has not been studied, therefore valsartan is not recommended in these patients. No dose adjustment is required for paediatric patients with a creatinine clearance >30 ml/min (see sections 4.2 and 5.2). Renal function and serum potassium should be closely monitored during treatment with valsartan. This applies particularly when valsartan is given in the presence of other conditions (fever, dehydration) likely to impair renal function.

Impaired hepatic function

As in adults, Diovan is contraindicated in paediatric patients with severe hepatic impairment, biliary cirrhosis and in patients with cholestasis (see sections 4.3 and 5.2). There is limited clinical experience with Diovan in paediatric patients with mild to moderate hepatic impairment. The dose of valsartan should not exceed 80 mg in these patients.

4.5 Interaction with other medicinal products and other forms of interactio

Dual blockade of the Renin-Angiotensin-Aldosterone System (RAAS) with ARBs, ACEIs, or aliskiren

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as

hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3, 4.4 and 5.1).

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 with Diovan. If the combination proves necessary, a careful monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may presumably be increased further.

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 considered necessary in combination with valsartan, monitoring of potassium plasma levels is advised.

Caution required with concomitant use

Non-steroidal anti-inflammatory medicines (NSAIDs), including selective COX-2 inhibitors, acetylsalicylic acid (>3 g/day), 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

In vitro data indicates that valsartan is a substrate of the hepatic uptake transporter OATP1B1/OATP1B3 and the hepatic efflux transporter MRP2. The clinical relevance of this finding is unknown. Co-administration of inhibitors of the uptake transporter (e.g. rifampin, ciclosporin) or efflux transporter (e.g. ritonavir) may increase the systemic exposure to valsartan. Exercise appropriate care when initiating or ending concomitant treatment with such drugs.

Others

In drug interaction studies with valsartan, no interactions of clinical significance have been found with valsartan or any of the following substances: cimetidine, warfarin, furosemide, digoxin, atenolol, indomethacin, hydrochlorothiazide, amlodipine, glibenclamide.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of Angiotensin II Receptor Antagonists (AIIIRAs) is not recommended during the first trimester of pregnancy (see section 4.4). The use of AIIIRAs is contraindicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however, a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with AIIIRAs, similar risks may exist for this class of drugs. Unless continued AIIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started.

AIIIRAs therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia); see also section 5.3 "Preclinical safety data".

Should exposure to AIIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Infants whose mothers have taken AIIIRAs should be closely observed for hypotension (see also sections 4.3 and 4.4).

Breast-feeding

Because no information is available regarding the use of valsartan during breastfeeding, Diovan 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

Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day. This dose is 6 times the maximum recommended human dose on a mg/m² basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive have been performed. When driving vehicles or operating machines it should be taken into account that dizziness or weariness may occur.

4.8 Undesirable effects

In controlled clinical studies in adult patients with hypertension, the overall incidence of adverse drug reactions (ADRs) was comparable with placebo and is consistent with the pharmacology of valsartan. The incidence of ADRs did not appear to be related to dose or treatment duration and also showed no association with gender, age or race.

The ADRs reported from clinical studies, post-marketing experience and laboratory findings are listed below according to system organ class.

Adverse Drug reactions

Adverse reactions are ranked by frequency, the most frequent first, using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (frequency cannot be estimated from the available data).

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

For all the ADRs reported from post-marketing experience and laboratory findings, it is not possible to apply any ADR frequency and therefore they are mentioned with a "not known" frequency.

Hypertension

| | |
|---|---|
| Blood and lymphatic system disorders | |
| Not known | Decrease in haemoglobin, Decrease in haematocrit, Neutropenia, Thrombocytopenia |
| Immune system disorders | |
| Not known | Hypersensitivity including serum sickness |
| Metabolism and nutrition disorders | |
| Not known | Increase of serum potassium, hyponatraemia |
| Ear and labyrinth disorders | |
| Uncommon | Vertigo |

| | |
|---|--|
| Vascular disorders | |
| Not known | Vasculitis |
| Respiratory, thoracic and mediastinal disorders | |
| Uncommon | Cough |
| Gastrointestinal disorders | |
| Uncommon | Abdominal pain |
| Hepato-biliary disorders | |
| Not known | Elevation of liver function values including increase of serum bilirubin |
| Skin and subcutaneous tissue disorders | |
| Not known | Angioedema, Dermatitis bullous, Rash, Pruritus |
| Musculoskeletal and connective tissue disorders | |
| Not known | Myalgia |
| Renal and urinary disorders | |
| Not known | Renal failure and impairment, Elevation of serum creatinine |
| General disorders and administration site conditions | |
| Uncommon | Fatigue |

The safety profile seen in controlled-clinical studies in adult patients with post-myocardial infarction and/or heart failure varies from the overall safety profile seen in hypertensive patients. This may relate to the patients underlying disease. ADRs that occurred in adult patients with post-myocardial infarction and/or heart failure patients are listed below.

Post-myocardial infarction and/or heart failure (studied in adult patients only)

Blood and lymphatic system disorders

| | |
|--|---|
| Not known | Thrombocytopenia |
| Immune system disorders | |
| Not known | Hypersensitivity including serum sickness |
| Metabolism and nutrition disorders | |
| Uncommon | Hyperkalaemia |
| Not known | Increase of serum potassium, hyponatraemia |
| Nervous system disorders | |
| Common | Dizziness, Postural dizziness |
| Uncommon | Syncope, Headache |
| Ear and labyrinth disorders | |
| Uncommon | Vertigo |
| Cardiac disorders | |
| Uncommon | Cardiac failure |
| Vascular disorders | |
| Common | Hypotension, Orthostatic hypotension |
| Not known | Vasculitis |
| Respiratory, thoracic and mediastinal disorders | |
| Uncommon | Cough |
| Gastrointestinal disorders | |
| Uncommon | Nausea, Diarrhea |
| Hepato-biliary disorders | |
| Not known | Elevation of liver function values |
| Skin and subcutaneous tissue disorders | |

| | |
|---|--|
| Uncommon | Angioedema |
| Not known | Dermatitis bullous, Rash, Pruritus |
| Musculoskeletal and connective tissue disorders | |
| Not known | Myalgia |
| Renal and urinary disorders | |
| Common | Renal failure and impairment |
| Uncommon | Acute renal failure, Elevation of serum creatinine |
| Not known | Increase in Blood Urea Nitrogen |
| General disorders and administration site conditions | |
| Uncommon | Asthenia, fatigue |

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

<https://sideeffects.health.gov.il>

4.9 Overdose

Symptoms

Over dosage with Diovan may result in marked hypotension, which could lead to depressed level of consciousness, circulatory collapse and/or shock.

Treatment

The therapeutic measures depend on the time of ingestion and the type and severity of the symptoms; stabilisation of the circulatory condition is of prime importance.

If hypotension occurs, the patient should be placed in a supine position and blood volume correction should be undertaken.

Valsartan is unlikely to be removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin II antagonists.plain, ATC code: C09CA03.

Valsartan is an orally active, potent and specific angiotensin II (Ang II) receptor antagonist. It acts selectively on the AT₁ receptor subtype, which is responsible for the known actions of angiotensin II. The increased plasma levels of Ang II following AT₁ receptor blockade with valsartan may stimulate the unblocked AT₂ receptor, 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 is not known to bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Valsartan does not inhibit ACE (also known as kininase II) which converts Ang I to Ang 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 ($P < 0.05$) less 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 cough compared to 68.5% of those treated with an ACE inhibitor ($P < 0.05$).

Hypertension (only 80 mg and 160 mg)

Administration of Diovan to patients with hypertension results in reduction of 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 reduction of blood pressure is achieved within 4-6 hours. The antihypertensive effect persists over 24 hours after dosing. During repeated dosing, the antihypertensive effect is substantially present within 2 weeks, and maximal effects are attained within 4 weeks and persist during long-term therapy. Combined with hydrochlorothiazide, a significant additional reduction in blood pressure is achieved.

Abrupt withdrawal of Diovan has not been associated with rebound hypertension or other adverse clinical events.

In hypertensive patients with type 2 diabetes and microalbuminuria, valsartan has been shown to reduce the urinary excretion of albumin. The MARVAL (Micro Albuminuria Reduction with Valsartan) study assessed the reduction in urinary albumin excretion (UAE) with valsartan (80-160 mg/od) versus amlodipine (5-10

mg/od), in 332 type 2 diabetic patients (mean age: 58 years; 265 men) with microalbuminuria (valsartan: 58 µg/min; amlodipine: 55.4 µg/min), normal or high blood pressure and with preserved renal function (blood creatinine <120 µmol/l). At 24 weeks, UAE was reduced ($p < 0.001$) by 42% (-24.2 µg/min; 95% CI: -40.4 to -19.1) with valsartan and approximately 3% (-1.7 µg/min; 95% CI: -5.6 to 14.9) with amlodipine despite similar rates of blood pressure reduction in both groups.

The Diovan Reduction of Proteinuria (DROP) study further examined the efficacy of valsartan in reducing UAE in 391 hypertensive patients (BP=150/88 mmHg) with type 2 diabetes, albuminuria (mean=102 µg/min; 20-700 µg/min) and preserved renal function (mean serum creatinine = 80 µmol/l). Patients were randomized to one of 3 doses of valsartan (160, 320 and 640 mg/od) and treated for 30 weeks. The purpose of the study was to determine the optimal dose of valsartan for reducing UAE in hypertensive patients with type 2 diabetes. At 30 weeks, the percentage change in UAE was significantly reduced by 36% from baseline with valsartan 160 mg (95%CI: 22 to 47%), and by 44% with valsartan 320 mg (95%CI: 31 to 54%). It was concluded that 160-320 mg of valsartan produced clinically relevant reductions in UAE in hypertensive patients with type 2 diabetes.

Recent myocardial infarction (40 mg, 80 mg and 160 mg)

The VALsartan In Acute myocardial iNfarcTion trial (VALIANT) was a randomized, controlled, multinational, double-blind study in 14,703 patients with acute myocardial infarction and signs, symptoms or radiological evidence of congestive heart failure and/or evidence of left ventricular systolic dysfunction (manifested as an ejection fraction $\leq 40\%$ by radionuclide ventriculography or $\leq 35\%$ by echocardiography or ventricular contrast angiography). Patients were randomized within 12 hours to 10 days after the onset of myocardial infarction symptoms to valsartan, captopril, or the combination of both. The mean treatment duration was two years. The primary endpoint was time to all-cause mortality.

Valsartan was as effective as captopril in reducing all-cause mortality after myocardial infarction. All-cause mortality was similar in the valsartan (19.9%), captopril (19.5%), and valsartan + captopril (19.3%) groups. Combining valsartan with captopril did not add further benefit over captopril alone. There was no difference between valsartan and captopril in all-cause mortality based on age, gender, race, baseline therapies or underlying disease. Valsartan was also effective in prolonging the time to and reducing cardiovascular mortality, hospitalization for heart failure, recurrent myocardial infarction, resuscitated cardiac arrest, and non-fatal stroke (secondary composite endpoint).

The safety profile of valsartan was consistent with the clinical course of patients treated in the post-myocardial infarction setting. Regarding renal function, doubling of serum creatinine was observed in 4.2% of valsartan-treated patients, 4.8 % of valsartan + captopril-treated patients and 3.4% of captopril-treated patients. Discontinuations due to various types of renal dysfunction occurred in 1.1% of valsartan-treated patients, 1.3% in valsartan + captopril patients, and 0.8% of

captopril patients. An assessment of renal function should be included in the evaluation of patients post-myocardial infarction.

There was no difference in all-cause mortality or cardiovascular mortality or morbidity when beta-blockers were administered together with the combination of valsartan + captopril, valsartan alone, or captopril alone. Irrespective of treatment, mortality was lower in the group of patients treated with a beta-blocker, suggesting that the known beta blocker benefit in this population was maintained in this trial.

Heart failure (40 mg, 80 mg and 160 mg)

Val-HeFT was a randomized, controlled, multinational clinical trial of valsartan compared with placebo on morbidity and mortality in 5,010 NYHA class II (62%), III (36%) and IV (2%) heart failure patients receiving usual therapy with LVEF <40% and left ventricular internal diastolic diameter (LVIDD) >2.9 cm/m². Baseline therapy included ACE inhibitors (93%), diuretics (86%), digoxin (67%) and beta blockers (36%). The mean duration of follow-up was nearly two years. The mean daily dose of Diovan in Val-HeFT was 254 mg. The study had two primary endpoints: all-cause mortality (time to death) and composite mortality and heart failure morbidity (time to first morbid event) defined as death, sudden death with resuscitation, hospitalization for heart failure, or administration of intravenous inotropic or vasodilator drugs for four hours or more without hospitalization.

All cause mortality was similar (p=NS) in the valsartan (19.7%) and placebo (19.4%) groups. The primary benefit was a 27.5% (95% CI: 17 to 37%) reduction in risk for time to first heart failure hospitalization (13.9% vs. 18.5%). Results appearing to favour placebo (composite mortality and morbidity was 21.9% in placebo vs. 25.4% in valsartan group) were observed for those patients receiving the triple combination of an ACE inhibitor, a beta blocker and valsartan.

In a subgroup of patients not receiving an ACE inhibitor (n=366), the morbidity benefits were greatest. In this subgroup all-cause mortality was significantly reduced with valsartan compared to placebo by 33% (95% CI: -6% to 58%) (17.3% valsartan vs. 27.1% placebo) and the composite mortality and morbidity risk was significantly reduced by 44% (24.9% valsartan vs. 42.5% placebo).

In patients receiving an ACE inhibitor without a beta-blocker, all-cause mortality was similar (p=NS) in the valsartan (21.8%) and placebo (22.5%) groups. Composite mortality and morbidity risk was significantly reduced by 18.3% (95% CI: 8% to 28%) with valsartan compared with placebo (31.0% vs. 36.3%).

In the overall Val-HeFT population, valsartan treated patients showed significant improvement in NYHA class, and heart failure signs and symptoms, including dyspnoea, fatigue, oedema and rales compared to placebo. Patients treated with valsartan had a better quality of life as demonstrated by change in the Minnesota Living with Heart Failure Quality of Life score from baseline at endpoint than placebo.

Ejection fraction in valsartan treated patients was significantly increased and LVIDD significantly reduced from baseline at endpoint compared to placebo.

Other: dual blockade of the renin-angiotensin-aldosterone system (RAAS)

Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker.

ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.

These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE inhibitors and angiotensin II receptor blockers. ACE inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

5.2 Pharmacokinetic properties

Absorption

Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2-4 hours. Mean absolute bioavailability for Diovan is 23%. Food decreases exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (C_{max}) 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 is not distributed into tissues extensively.

Valsartan is highly bound to serum protein (94-97%), mainly serum albumin.

Biotransformation

Valsartan is not biotransformed 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 ($t_{1/2\alpha} < 1\text{h}$ and $t_{1/2\beta}$ about 9 h). Valsartan is primarily eliminated by biliary excretion in faeces (about 83% of dose) and renally in 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.

In heart failure patients (40mg,80 mg, 160mg):

The average time to peak concentration and elimination half-life of valsartan in heart failure patients are similar to that observed in healthy volunteers. AUC and C_{\max} values of valsartan are almost proportional with increasing dose over the clinical dosing range (40 to 160 mg twice a day). The average accumulation factor is about 1.7. The apparent clearance of valsartan following oral administration is approximately 4.5 L/h. Age does not affect the apparent clearance in heart failure patients.

Special populations

Older people

A somewhat higher systemic exposure to valsartan was observed in some elderly subjects than in young subjects; and a lower starting dose (40 mg) is recommended for the elderly.

Impaired renal function

As expected for a compound where renal clearance accounts for only 30% of total plasma clearance, no correlation was seen between renal function and systemic exposure to valsartan. Dose adjustment is therefore not required in patients with renal impairment (creatinine clearance - $>10\text{ ml/min}$).

There is currently no experience on the safe use in patients with a creatinine clearance $<10\text{ ml/min}$ and patients undergoing dialysis, therefore valsartan should be used with caution in these patients (see sections 4.2 and 4.4).

Valsartan is highly bound to plasma protein and is unlikely to be removed by dialysis.

Hepatic impairment

Approximately 70% of the dose absorbed is eliminated in the bile, essentially in the unchanged form. Valsartan does not undergo any noteworthy biotransformation. A doubling of exposure (AUC) was observed in patients with mild to moderate hepatic impairment compared to healthy subjects. However, no correlation was observed

between plasma valsartan concentrations versus degree of hepatic dysfunction. Diovan has not been studied in patients with severe hepatic dysfunction (see sections 4.2, 4.3 and 4.4).

Impaired renal function

Use in paediatric patients with a creatinine clearance <30 ml/min and paediatric patients undergoing dialysis has not been studied, therefore valsartan is not recommended in these patients. No dose adjustment is required for paediatric patients with a creatinine clearance >30 ml/min. Renal function and serum potassium should be closely monitored (see sections 4.2 and 4.4).

5.3 Preclinical safety data

None-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential.

In rats, maternally toxic doses (600 mg/kg/day) during the last days of gestation and lactation led to lower survival, lower weight gain and delayed development (pinna detachment and ear-canal opening) in the offspring (see section 4.6). These doses in rats (600 mg/kg/day) are approximately 18 times the maximum recommended human dose on a mg/m² basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient).

In none-clinical safety studies, high doses of valsartan (200 to 600 mg/kg body weight) caused in rats a reduction of red blood cell parameters (erythrocytes, haemoglobin, haematocrit) and evidence of changes in renal haemodynamics (slightly raised plasma urea, and renal tubular hyperplasia and basophilia in males). These doses in rats (200 and 600 mg/kg/day) are approximately 6 and 18 times the maximum recommended human dose on a mg/m² basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient).

In marmosets at similar doses, the changes were similar though more severe, particularly in the kidney where the changes developed to a nephropathy which included raised urea and creatinine.

Hypertrophy of the renal juxtaglomerular cells was also seen in both species. All changes were considered to be caused by the pharmacological action of valsartan which produces prolonged hypotension, particularly in marmosets. For therapeutic doses of valsartan in humans, the hypertrophy of the renal juxtaglomerular cells does not seem to have any relevance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose

Crospovidone

Magnesium stearate

Colloidal anhydrous silica

Film coat

Hypromellose

Titanium dioxide (E171)

Macrogol 8000

Iron oxide red (E172)

Iron oxide yellow (E172)

Iron oxide black (E172; 40 mg and 160 mg tablets only)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

6.4 Special precautions for storage

Store below 30°C. Store in the original package in order to protect from moisture.

Diovan must be kept out of the reach and sight of children.

6.5 Nature and contents of container

40 mg: PVC/PA/Alu or PVC/PE/PVDC/Alu blisters

Pack sizes: 14 or 28 film-coated tablets

80 mg: PVC/PA/Alu blisters

Pack sizes: 14, 28, 56 and 98 film-coated tablets

160 mg: PVC/PA/Alu blisters

Pack sizes: 14, 28, 56 and 98 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. Registration Holder and importer:

Novartis Israel Ltd., P.O.B. 7126, Tel Aviv, Israel.

This leaflet was revised on October 2020