NOVARTIS

DIOVAN®

40, 80, 160, 320 MG

Film-coated Tablets

(Valsartan)

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1. NAME OF THE MEDICINE

DIOVAN® 40

(Film-coated tablet)

DIOVAN® 80 TABLETS

(Film-coated tablet)

DIOVAN® 160 TABLETS

(Film-coated tablet)

DIOVAN® 320 TABLETS

(Film-coated tablet)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 40 mg, 80 mg, 160 mg or 320 mg valsartan.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film Coated tablets (FCT)

DIOVAN® 40 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.

Length: approximately 9,1 mm

Width: approximately 3,5 mm

The score line on one side of DIOVAN 40 mg film-coated tablet is to divide the tablet into equal doses.

DIOVAN® 80 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.

Diameter: approximately 8,2 mm

DIOVAN® 160 Tablet:

Grey-orange, ovaloid film-coated tablet, slightly convex, scored on one side with debossing “DX” on one side of the score and “DX” on the other side of the score and “NVR” on the reverse side of the tablet.

Length: approximately 14,2 mm

Width: approximately 5,7 mm

DIOVAN® 320 Tablet:

Dark grey violet, ovaloid film-coated tablet with bevelled edges, slightly convex, scored on one side with debossing “DC” on one side of the score and “DC” on the other side of the score and “NVR” on the reverse side of the tablet.

Length: approximately 17,6 mm

Width: approximately 8,1 mm

The score line on one side of DIOVAN 80 mg, 160 mg or 320 mg tablet is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hypertension:

Treatment of mild to moderate essential hypertension in adult patients 18 years and older.

Post-myocardial infarction:

To improve survival following a recent (12 hours – 10 days) myocardial infarction in clinically stable patients with signs, symptoms, or radiological evidence of left ventricular failure and/or with left ventricular systolic dysfunction.

Heart Failure:

DIOVAN is indicated for the treatment of heart failure (NYHA class II – IV).

4.2 Posology and method of administration

Posology:

Hypertension:

The recommended dose of DIOVAN is 80 mg or 160 mg once daily.

The antihypertensive effect is substantially present within 2 weeks and maximal effects are seen after 4 weeks. In patients whose blood pressure is not adequately controlled, the daily dose may be increased to 320 mg, or a diuretic may be added.

DIOVAN may also be administered with other antihypertensive medicines.

Post-myocardial infarction:

Therapy may be initiated as early as 12 hours after a myocardial infarction. After an initial dose of 20 mg twice daily, DIOVAN 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.

The target dose is 160 mg twice daily. In general, it is recommended that patients achieve a dose level of 80 mg twice daily by two weeks after treatment initiation and that the target maximum dose be achieved by three months, based on the patient's tolerability to valsartan during titration. If symptomatic hypotension or renal dysfunction occurs, consideration should be given to a dosage reduction.

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

Evaluation of post-myocardial infarction patients should always include assessment of renal function.

Heart failure:

The recommended starting dose of DIOVAN is 40 mg twice daily. Up-titration to 80 mg and 160 mg twice daily should be done to the highest dose, 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.

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

Special population

Renal impairment

No dosage adjustment is required for patients with mild to moderate renal impairment (where the creatinine clearance is 30 to less than 90 mL/min). A lower dose should be considered for patients with a history of hepatic impairment (see section 4.4).

Paediatric population

The safety and efficacy of DIOVAN have not been established in children.

Currently available data are described in section 5.1 and 5.2, but no recommendation on a posology can be made.

Method of administration:

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

4.3 Contraindications

- Hypersensitivity to valsartan or any of the excipients of DIOVAN
- A history of angioedema related to previous therapy with ACE inhibitors or angiotensin receptor blockers (ARBs): These patients must never again be given these medicines
- Hereditary or idiopathic angioedema
- Hypertrophic obstructive cardiomyopathy (HOCM)
- Pregnancy and lactation (see section 4.6)
- Severe renal function impairment (CrCl < 30 mL/min)
- Aortic valve stenosis
- Mitral valve stenosis
- Bilateral renal artery stenosis
- Renal artery stenosis in patients with a single kidney
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride (see section 4.5)
- Porphyria
- Lithium therapy: Concomitant administration with DIOVAN may lead to toxic serum concentrations of lithium (see section 4.5)
- Concomitant use of DIOVAN with aliskiren in patients with Type 2 diabetes mellitus (see section 4.5, subsection dual blockade of the RAAS)
- Concomitant use of DIOVAN with aliskiren-containing products in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1,73 m^2) (see sections 4.5 and 5.1)
- Concomitant use of fluoroquinolones with ACE inhibitors/Angiotensin receptor blockers is contraindicated in patients with moderate to severe renal impairment (Creatinine Clearance ≤ 30 mL/min) and in elderly patients.

4.4 Special warnings and precautions for use

Should a woman become pregnant while treated with DIOVAN, the treatment should be stopped promptly and switched to a different class of antihypertensive medicines. (see section 4.6)

Sodium- and/or volume-depleted patients:

In sodium-depleted and/or volume-depleted patients, such as those receiving high doses of diuretics, and/or patients with moderate to severe renal impairment, symptomatic hypotension may occur 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.

If hypotension occurs, 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 stabilised.

Renal artery stenosis:

Since other medicines that affect the renin-angiotensin-aldosterone system (RAAS) may increase serum urea and serum creatinine in patients with bilateral or unilateral renal artery stenosis. Monitoring of both parameters is recommended as a safety measure. DIOVAN should not be used in patients with bilateral renal artery stenosis or unilateral renal artery stenosis of an artery to a single kidney, aortic valve stenosis, mitral valve stenosis or hypertrophic obstructive cardiomyopathy (see section 4.3).

Impaired renal function:

No dosage adjustment is required for patients with mild to moderate renal impairment (where the creatinine clearance is above 30 to ≤ 90 mL/min).

DIOVAN is contraindicated in patients with severe renal function impairment (CrCl < 30mL/min).

The use of DIOVAN with aliskiren should be avoided in patients with renal impairment (GFR < 60 mL/min) (see section 4.5, subsection dual blockade of the RAAS).

Concomitant use with fluoroquinolones

The concomitant use of fluoroquinolones with ACE inhibitors/Angiotensin receptor blockers is contraindicated in patients with moderate to severe renal impairment (Creatinine Clearance < 30 mL/min) and in elderly patients.

Renal function should be assessed before initiating treatment and monitored during treatment with fluoroquinolones or ACE inhibitors/Angiotensin receptor blockers whether used separately and/or concomitantly.

Patients currently treated with concomitant use of ACE inhibitors/Angiotensin receptor blockers and fluoroquinolones should contact their doctor to re-evaluate their treatment.

Hepatic impairment:

No dosage adjustment is required for patients with hepatic insufficiency. DIOVAN is mostly eliminated unchanged in the bile, and patients with biliary obstructive disorders showed lower DIOVAN clearance (see section 5.2). Particular caution should be exercised when administering valsartan to patients with biliary obstructive disorders.

Post-myocardial infarction/Heart failure:

Use of DIOVAN in patients with post-myocardial infarction or heart failure, commonly results in some reduction in blood pressure, but discontinuation of DIOVAN therapy because of continuing symptomatic hypotension is not usually necessary provided dosing instructions are followed.

Caution should be observed when initiating therapy in patients with heart failure or post myocardial infarction (see section 4.2).

As a consequence of inhibiting the renin-angiotensin-aldosterone system (RAAS), 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 RAAS, treatment with ACE inhibitors or angiotensin receptor antagonists has been associated with oliguria and/or progressive azotaemia and (rarely) with acute renal failure and/or death. Evaluation of patients with post-myocardial infarction and heart failure should always include assessment of renal function.

In patients with heart failure, caution should be observed with concurrent administration of ACE inhibitors, beta-blockers, and DIOVAN as an increase in mortality has been reported on this triple therapy.

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.

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

Caution is required while co-administering ARBs, including DIOVAN, with other medicines blocking the RAAS such as ACEIs or aliskiren (see section 4.5 and 4.3).

4.5 Interaction with other medicines and other forms of interaction

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

The concomitant use of DIOVAN, with other medicines acting on the RAAS is associated with an increased incidence of hypotension, hyperkalaemia, and changes in renal function compared to monotherapy. It is recommended to monitor blood pressure, renal function, and electrolytes in patients on DIOVAN and other medicines that affect the RAAS (see section 4.4).

The concomitant use of DIOVAN with aliskiren, should be avoided in patients with renal impairment (GFR < 60 mL/min) (see section 4.4).

The concomitant use of DIOVAN with aliskiren is contraindicated in patients with Type 2 diabetes mellitus or renal impairment (GFR < 60 mL/min/1.73 m^2) (see section 4.3).

Potassium:

Concomitant use of potassium-sparing diuretics (e.g. spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium that may lead to increases in serum potassium, and in patients with heart failure, to increase in serum creatinine, are contraindicated. If needed, serum potassium to be monitored.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors):

When angiotensin II antagonists are administered simultaneously with NSAIDs, attenuation of the antihypertensive effect may occur.

Furthermore, in elderly patients, volume-depleted (including those on diuretic therapy), or with compromised renal function, concomitant use of angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function. Therefore, monitoring of renal function is recommended when initiating or modifying the treatment in patients on valsartan who are taking NSAIDs concomitantly.

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported. Concurrent use of lithium and valsartan as contained in DIOVAN, is contraindicated. Therefore, monitoring of serum lithium levels is recommended, if needed (see section 4.3).

Transporters

The results from an *in vitro* study with human liver tissue indicate that valsartan is a substrate of the hepatic uptake transporter OATP1B1 and the hepatic efflux transporter MRP2. 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.

No drug interactions of clinical significance have been found. Compounds studied in clinical trials include cimetidine, warfarin, furosemide, digoxin, atenolol, indomethacin, hydrochlorothiazide, amlodipine and glibenclamide.

As DIOVAN is not metabolised to a significant extent, clinically relevant drug-drug interactions in the form of metabolic induction or inhibition of the cytochrome P450 system are not expected with valsartan. Although valsartan is highly bound to plasma proteins, *in vitro* studies have not shown any interaction at this level with a range of molecules which are also highly protein-bound, such as diclofenac, furosemide, and warfarin.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

DIOVAN acts directly on the RAAS and therefore should not be used in women planning to become pregnant. Healthcare professionals prescribing DIOVAN should counsel women of childbearing potential about the potential risk during pregnancy.

Pregnancy

When pregnancy is detected, DIOVAN should be discontinued as soon as possible. Not to be used in pregnancy as teratogenicity has been shown in experimental animals.

Safety in pregnancy and lactation has not been established (see section 4.3).

In case of accidental exposure to ARB therapy, appropriate foetal monitoring should be considered.

Infants whose mothers have taken DIOVAN should be closely observed for hypotension.

There have been reports of spontaneous abortion, oligohydramnios, and newborn renal dysfunction when pregnant women have inadvertently taken valsartan.

Breastfeeding

It is not known whether valsartan is excreted in human milk. Since valsartan was excreted in the milk of lactating rats, mothers taking DIOVAN should not breastfeed their infants.

Fertility

There is no information on the effects of DIOVAN on human fertility. Studies in rats did not show any effects of valsartan on fertility.

4.7 Effects on ability to drive and use machines

When driving vehicles or operating machines it should be taken into account that dizziness or weariness may occur.

It is advisable to exercise caution when driving or operating machinery.

4.8 Undesirable effects

Frequencies are defined as: very common (≥ 1/10); Common (≥ 1/100, <1/10); uncommon (≥ 1/100, < 1/1 000); rare (≥ 1/10 000, < 1/1 000); very rare (< 1/10 000).

Table 1: Adverse drug reactions in Hypertension from clinical trials

Ear and labyrinth system disorders	
Uncommon	Vertigo
Respiratory, thoracic, and mediastinal disorders	
Uncommon	Cough
Gastrointestinal disorders	
Uncommon	Abdominal pain
General disorders and administration site conditions	
Uncommon	Fatigue

The following events have also been observed during clinical trials in hypertensive patients irrespective of their causal association with the study drug: Arthralgia, asthenia, back pain, diarrhoea, dizziness, headache, insomnia, libido decrease, nausea, oedema, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection, viral infections.

Heart failure and/or post-myocardial infarction

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

Table 2: Adverse drug reactions in heart failure and/or post-myocardial infarction from clinical trials

Metabolism and nutrition disorders	
Uncommon	Hyperkalaemia
Nervous system disorders	
Common	Dizziness, postural dizziness
Uncommon	Syncope, headache

Ear and labyrinth system disorders	
Uncommon	Vertigo
Cardiac disorders	
Uncommon	Cardiac failure
Vascular disorders	
Common	Hypotension, orthostatic hypotension
Respiratory, thoracic, and mediastinal disorders	
Uncommon	Cough
Gastrointestinal disorders	
Uncommon	Nausea, diarrhoea
Skin and subcutaneous tissue disorders	
Uncommon	Angioedema
Renal and urinary disorders	
Common	Renal failure and impairment
Uncommon	Acute renal failure, serum creatinine increased
General disorders and administration site conditions	
Uncommon	Asthenia, fatigue

The following events have also been observed during clinical trials in patients with heart failure and/or post-myocardial infarction irrespective of their causal association with the study drug: Arthralgia, abdominal pain, back pain, insomnia, libido decrease, neutropenia, oedema, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection, viral infections.

Post-marketing adverse drug reactions

Table 1: Adverse drug reactions in Hypertension from post-marketing experience

Blood and lymphatic system disorders	
Not known	Haemoglobin decreased, haematocrit decreased, neutropenia, thrombocytopenia
Immune system disorders	
Not known	Hypersensitivity including serum sickness
Metabolism and nutrition disorders	
Not known	Serum potassium increased
Vascular disorders	
Not known	Vasculitis
Hepato-biliary disorders	
Not known	Liver function test abnormal including serum bilirubin increase
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, serum creatinine increased

Table 2: Adverse drug reactions in heart failure and/or post-myocardial infarction from post-marketing experience

Blood and lymphatic system disorders	
Not known	Thrombocytopenia
Immune system disorders	

Not known	Hypersensitivity including serum sickness
Metabolism and nutrition disorders	
Uncommon	Hyperkalaemia
Vascular disorders	
Not known	Vasculitis
Hepato-biliary disorders	
Not known	Liver function test abnormal
Skin and subcutaneous tissue disorders	
Not known	Dermatitis bullous, rash, pruritus
Musculoskeletal and connective tissue disorders	
Not known	Myalgia
Renal and urinary disorders	
Not known	Serum urea increased

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Overdose with DIOVAN may result in marked hypotension, which could lead to depressed level of consciousness, circulatory collapse and/or shock. If the ingestion is recent, vomiting should be induced if the patient is conscious. Otherwise, the usual treatment would be intravenous infusion of normal saline solution.

DIOVAN is unlikely to be removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification

A 7.1.3 Vascular medicines – other hypotensives

Valsartan is an orally active, specific angiotensin II (Ang II) receptor antagonist. It acts selectively on the angiotensin 1 (AT_1) receptor subtype, which is responsible for the known actions of angiotensin II. The increased plasma levels of Ang II following AT_1 receptor blockade with valsartan may stimulate the unblocked AT_2 receptor, which appears to counterbalance the effect of the AT_1 receptor. Valsartan does not exhibit any partial agonist activity at the AT_1 receptor and has much greater affinity (about 20 000-fold) for the AT_1 receptor than for the AT_2 receptor.

The angiotensin 2 (AT_2) receptor subtype is unrelated to cardiovascular effect.

Hypertension:

Administration of valsartan 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 to 6 hours. The antihypertensive effect persists for over 24 hours after dosing. During repeated dosing, the maximum reduction in blood pressure with any dose is generally attained within 2 to 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.

Post-myocardial infarction:

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.

Patients were randomized after the onset of myocardial infarction symptoms to one of three treatment groups: valsartan was up titrated from 20 mg twice daily to highest tolerated dose up to a maximum of 160 mg twice daily.

Baseline therapy included acetylsalicylic acid (91 %), beta-blockers (70 %), ACE inhibitors (40 %), thrombolytics (35 %), and statins (34 %).

Valsartan was effective in reducing all-cause mortality after myocardial infarction.

Valsartan was also effective in reducing cardiovascular mortality, hospitalisation for heart failure, recurrent myocardial infarction and in improving time to the first morbid event of cardiovascular death.

Heart Failure:

In heart failure patients untreated with ACE inhibitors for at least 6 months, valsartan improved pulmonary capillary wedge pressure (PCWP), systemic vascular resistance (SVR), cardiac output (CO) and seated blood pressure (SBP) after 28 days of treatment.

5.2 Pharmacokinetic properties

Absorption

Valsartan is absorbed after oral administration, although the amount absorbed varies widely. Mean absolute bioavailability for valsartan is 23 %. When valsartan is given with food, the area under the plasma concentration curve (AUC) of valsartan is reduced by 48 %, although from about 8 hours post dosing plasma

valsartan concentrations are similar for the fed and fasted group. This reduction in AUC, however, is not accompanied by a clinically significant reduction in the therapeutic effect, and valsartan can therefore be given either with or without food.

Distribution

Valsartan is highly bound to serum protein (94 % to 97 %), mainly serum albumin. Steady-state volume of distribution after intravenous administration is low (about 17 L) indicating that valsartan is not distributed into tissues extensively.

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 multi exponential decay kinetics (t½ α < 1 h and t½ β about 9 h). Plasma clearance is relatively slow (about 2 L/h) when compared with hepatic blood flow (about 30 L/h). Of the absorbed dose of valsartan 70 % is excreted in the faeces and after iv administration, 30 % in the urine, mainly as unchanged compound. The half-life of valsartan is 6 hours.

The pharmacokinetics of valsartan is linear in the dose range tested. There is no change in the kinetics of valsartan on repeated administration and little accumulation when dosed once daily. Plasma concentrations are similar in males and females.

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 increase linearly and 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 approximately 4,5 L/h. Age does not affect the apparent clearance in heart failure patients.

Elderly:

A significantly higher systemic exposure to valsartan was observed in elderly subjects than in young subjects; however, this has not been shown to have any clinical significance.

Impaired Renal Function:

Renal clearance accounts for only 30 % of total plasma clearance and no correlation is seen between renal function and systemic exposure to valsartan. Dose adjustment is therefore not required in patients with mild renal impairment. No studies have been performed in patients undergoing dialysis. However, valsartan is highly bound to plasma protein and is unlikely to be removed by dialysis.

Hepatic impairment:

About 70 % of the absorbed dose is excreted in the bile mainly as unchanged compound. Valsartan does not undergo extensive biotransformation and systemic exposure to valsartan is not correlated with the degree of liver dysfunction. No dose adjustment for valsartan is therefore necessary in patients with hepatic insufficiency of non-biliary origin and without cholestasis. The AUC with valsartan has been observed to be approximately double in patients with biliary cirrhosis or biliary obstruction (see section 4.4).

Paediatric population

In a study of 26 paediatric hypertensive patients (aged 1 to 16 years) given a single dose of a suspension of valsartan (mean: 0,9 to 2 mg/kg, with a maximum dose of 80 mg), the clearance (litres/h/kg) of valsartan was comparable across the age range of 1 to 16 years and similar to that of adults receiving the same formulation (see section 4.4).

5.3 Preclinical safety data

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, carcinogenic potential and effects on fertility.

Safety pharmacology and long-term toxicity

In a variety of preclinical safety studies conducted in several animal species, there were no findings that would exclude the use of therapeutic doses of valsartan in humans.

In preclinical safety studies, high doses of valsartan (200 to 600 mg/kg/day body weight) caused in rats a reduction of red blood cell parameters (erythrocytes, haemoglobin, haematocrit) and evidence of changes in renal haemodynamics (slightly raised serum 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/m^2 basis (calculations assume an oral dose of 320 mg/day and a 60 kg patient). In marmosets at comparable doses, the changes were similar though more severe, particularly in the kidney where the changes developed to a nephropathy including raised serum urea and serum 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.

Reproductive toxicity

In a rat fertility study, valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day, approximately 18 times the maximum recommended human dose on a mg/m^2 basis (calculations assume an oral dose of 320 mg/day and a 60 kg patient).

Mutagenicity

Valsartan was devoid of mutagenic potential at either the gene or chromosome level when investigated in various standard *in vitro* and *in vivo* genotoxicity studies.

Carcinogenicity

There was no evidence of carcinogenicity when valsartan was administered in the diet to mice and rats for 2 years at doses up to 160 and 200 mg/kg/day, respectively.

Paediatric population

Daily oral dosing of neonatal/juvenile rats (from a postnatal day 7 to postnatal day 70) with valsartan at doses as low as 1 mg/kg/day (about 10 % to 35 % of the maximum recommended paediatric dose of approximately 4 mg/kg/day on systemic exposure basis) produced persistent, irreversible kidney damage. The effects mentioned above represent an expected exaggerated pharmacological effect of angiotensin converting enzyme inhibitors and angiotensin II type 1 blockers; such effects are observed if rats are treated during the first 13 days of life. This period coincides with 36 weeks of gestation in humans, which could occasionally extend up to 44 weeks after conception in humans. The rats in the juvenile valsartan study were dosed up to day 70, and effects on renal maturation (postnatal 4 to 6 weeks) cannot be excluded. Functional renal maturation is an ongoing process within the first year of life in humans. Consequently, a clinical relevance in children <1 year of age cannot be excluded, while preclinical data do not indicate a safety concern for children older than 1 year.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose, crospovidone, colloidal anhydrous silica, magnesium stearate, hypromellose, titanium dioxide (E171), Macrogol 8000, red iron oxide (E172), yellow iron oxide (E172), black iron oxide (E172; 40 mg ,160 mg and 320 mg only).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

40 mg and 320 mg – 24 months

80 mg and 160 mg – 36 months

6.4 Special precautions for storage

Store at or below 30 °C. Protect from moisture.

KEEP OUT OF THE REACH OF CHILDREN.

6.5 Nature and contents of container

28 tablets in polyvinyl chloride/polyethylene/polyvinyldichloride (PVC/PE/PVDC)/ aluminium foil blisters or polyamide/aluminium/polyvinylchloride (PA/AL/PVC)/ aluminium foil blisters.

The outer container is a printed cardboard box.

6.6 Special precautions for disposal and other handling

No specific requirements for disposal.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Novartis South Africa (Pty) Ltd.

Magwa Crescent West

Waterfall City

Jukskei view

Johannesburg,

2090

8. REGISTRATION NUMBERS

DIOVAN® 40: 36/7.1.3/0382

DIOVAN® 80 Tablets: 36/7.1.3/0034

DIOVAN® 160 Tablets: 36/7.1.3/0035

DIOVAN® 320 Tablets: 40/7.1.3/0542

9. DATE OF FIRST AUTHORISATION

30 November 2007

10. DATE OF REVISION OF THE TEXT

09 October 2023