DIOVAN RANGE PACKAGE INSERT

SCHEDULING STATUS S3

PROPRIETARY NAMES (AND DOSAGE FORMS)
DIOVAN® 40
(film-coated tablet)
DIOVAN® 80 Tablet
(film-coated tablet)
DIOVAN® 160 Tablet
(film-coated tablet)
DIOVAN® 320
(film-coated tablet)

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

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).

PHARMACOLOGICAL CLASSIFICATION
A 7.1.3 Vascular medicines – other hypotensives

PHARMACOLOGICAL ACTION
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 uptitrated 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.

Pharmacokinetics:
Valsartan is absorbed after oral administration, although the amount absorbed varies widely. Mean absolute bioavailability for valsartan is 23 %. Valsartan shows multi-exponential decay kinetics ($t_{½}\ \alpha$ < 1 h and $t_{½}\ \beta$ about 9 h).

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.

Valsartan is highly bound to serum protein (94 to 97 %), mainly serum albumin. Steady-state volume of distribution is low (about 17 L). 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.

When valsartan is given with food, the area under the plasma concentration curve (AUC) of valsartan is reduced by 48 %, although from about 8 h 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.

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 *Special precautions*).

INDICATIONS
Hypertension:
Treatment of mild to moderate hypertension.

Post-myocardial infarction:
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.

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

CONTRA-INDICATIONS
Hypersensitivity to valsartan or any of the excipients of DIOVAN.

Pregnancy and lactation (see *Pregnancy and lactation*).

Moderate to severe renal function impairment.

WARNINGS
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.

INTERACTIONS
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.

Concomitant use of potassium-sparing diuretics (e.g. spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium, and in heart failure patients to increase in serum creatinine. If co-medication is considered necessary, caution is advisable.

PREGNANCY AND LACTATION
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.

DOSAGE AND DIRECTIONS FOR USE
Hypertension:
The recommended dose of DIOVAN is 80 mg or 160 mg once daily, irrespective of race, age or gender.

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 agents.

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.

NOTE for all indications: No dosage adjustment is required for patients with mild renal impairment (where the creatinine clearance is above 70 ml/min) or for patients with hepatic insufficiency of non-biliary origin and without cholestasis.

Use in children and adolescents:
The safety and efficacy of DIOVAN have not been established in children and adolescents (below the age of 18 years).

SIDE-EFFECTS AND SPECIAL PRECAUTIONS
Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1 000, < 1/100); rare (≥ 1/10 000, < 1/1 000); very rare (< 1/10 000).

Table 1:

Infections and infestations:	
Common:	Viral infections
Uncommon:	Upper respiratory tract infection, pharyngitis, sinusitis
Very rare:	Rhinitis
Blood and lymphatic system disorders:	
Common:	Neutropenia
Very rare:	Thrombocytopenia
Immune system disorders:	
Very rare:	Hypersensitivity including serum sickness
Metabolism and nutrition disorders:	
Uncommon:	Hyperkalaemia*[#]
Psychiatric disorders:	
Uncommon:	Insomnia, libido decrease
Nervous system disorders:	
Common:	Postural dizziness[#]
Uncommon:	Syncope*
Rare:	Dizziness[##]
Very rare:	Headache[##]
Ear and labyrinth disorders:	
Uncommon:	Vertigo
Cardiac disorders:	
Uncommon:	Cardiac failure*
Vascular disorders:	
Common:	Orthostatic hypotension[#]
Uncommon:	Hypotension*[##]
Very rare:	Vasculitis
Respiratory, thoracic and mediastinal disorders:	
Uncommon:	Cough

Gastrointestinal disorders:	
Uncommon:	Diarrhoea, abdominal pain
Very rare:	Nausea[##]
Skin and subcutaneous tissue disorders:	
Very rare:	Angioneurotic oedema**, rash, pruritus
Musculoskeletal and connective tissue disorders:	
Uncommon:	Back pain
Very rare:	Arthralgia, myalgia
Renal and urinary disorders:	
Very rare:	Renal impairment**[##], acute renal failure**, renal insufficiency**
General disorders and administration site conditions:	
Uncommon:	Fatigue, asthenia, oedema

*reported in post-myocardial infarction indication
[#]reported in heart failure indication
**reported as uncommon in post-myocardial infarction indication
[##]reported more frequently in heart failure indication (common: dizziness, renal impairment, hypotension; uncommon: headache, nausea)

Laboratory findings:
DIOVAN may be associated with decreases in haemoglobin and haematocrit.

Neutropenia was observed in 1,9 % of patients treated with DIOVAN versus 1,6 % of patients treated with an ACE inhibitor.

In controlled clinical trials in hypertensive patients, significant increases in serum creatinine, potassium and total bilirubin were observed, respectively, in 0,8 %, 4,4 %, and 6 % of patients treated with DIOVAN versus 1,6 %, 6,4 % and 12,9 % of those treated with an ACE inhibitor.

No special monitoring of laboratory parameters is necessary for patients with essential hypertension receiving DIOVAN therapy.

Occasional elevations of liver function values were reported in hypertensive patients treated with DIOVAN.

Special precautions:
Renal artery stenosis:
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 or serum creatinine. However, since other drugs that affect the renin-angiotensin-aldosterone system may increase blood urea and serum creatinine in patients with bilateral or unilateral renal artery stenosis, monitoring of both parameters is recommended as a safety measure.

Impaired renal function:
No dosage adjustment is required for patients with mild renal impairment. However, in moderate to severe cases (creatinine clearance < 70 ml/min) insufficient data is available. DIOVAN should not be used because of increased side-effects.

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 *Pharmacokinetics*). 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 *Dosage and directions for use*).

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.

Effects on ability to drive and use machines:
It is advisable to exercise caution when driving or operating machinery.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT
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. Otherwise, the usual treatment would be intravenous infusion of normal saline solution.

DIOVAN is unlikely to be removed by haemodialysis.

IDENTIFICATIONS
DIOVAN® 40 Tablet:
Yellow, ovaloid with bevelled edges, scored on one side with debossing “DO” on the scored side and “NVR” on the other side.

DIOVAN® 80 Tablet:
Pale red, round film-coated tablet with bevelled edges, imprinted “D/V” on the one side and “NVR” on the other side.

DIOVAN® 160 Tablet:
Grey-orange, ovaloid film-coated tablet, imprinted **“**DX**”** on the one side and “NVR” on the other side.

DIOVAN® 320 Tablet:
Dark grey-violet, ovaloid film-coated tablet with bevelled edges, imprinted **“**DXL**”** on the one side and “NVR” on the other side.

PRESENTATIONS
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.

STORAGE INSTRUCTIONS
Store at or below 30 °C. Protect from moisture.
KEEP OUT OF THE REACH OF CHILDREN.

REGISTRATION NUMBERS
DIOVAN® 40: 36/7.1.3/0382
DIOVAN® 80 Tablet: 36/7.1.3/0034
DIOVAN® 160 Tablet: 36/7.1.3/0035
DIOVAN® 320: 40/7.1.3/0542

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	Botswana		Namibia	
Diovan ® 40 mg	N/A	S2	05/7.1.3/0429	NS2
Diovan ® 80 mg	BOT0400602	S2	05/7.1.3/0377	NS2
Diovan ® 160 mg	BOT0400603	S2	05/7.1.3/0378	NS2
Diovan ® 320 mg	BOT1302389C	S2	08/7.1.3/0216	NS2

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