

SUMMARY OF PRODUCT CHARACTERISTICS

Summary of Product Characteristics

DIOVAN[®] (valsartan)

40 mg, 80 mg, 160 mg, 320 mg Film-coated tablets
3 mg/mL Oral solution

Diovan[®]

Angiotensin II antagonist

DESCRIPTION AND COMPOSITION

Pharmaceutical forms

Film-coated tablet.

Diovan 40 mg: Yellow, ovaloid with bevelled edges, scored on one side; with debossing “DO” on the scored side and “NVR” on the other side

Diovan 80 mg: Pale red, round with bevelled edges, scored on one side; with debossing “D/V” on the scored side and “NVR” on the other side

Diovan 160 mg: Grey-orange, ovaloid, scored on one side; with debossing “DX/DX” on the scored side and “NVR” on the other side

Diovan 320 mg: Dark grey-violet, ovaloid with bevelled edges with debossing “DXL” on one side and “NVR” on the other side.

Oral Solution: Clear, colorless to pale yellow solution

Appearance of tablets may differ between countries. Certain dosage strengths and dosage forms may not be available in all countries.

Active substance

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

Each mL oral solution contains 3 mg of valsartan.

Excipients

Tablets: 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 tablets only), brown iron oxide (mixture of red iron oxide and black iron oxide (320 mg tablets only).

Oral Solution: sucrose, methyl parahydroxybenzoate (E218), potassium sorbate, poloxamer (188), citric acid, anhydrous, sodium citrate, artificial blueberry flavour (538926 C), propylene glycol (E1520), sodium hydroxide, hydrochloric acid, purified water

Pharmaceutical formulations may vary between countries.

INDICATIONS

Hypertension

Treatment of hypertension in adults and in children and adolescents 6-18 years of age.

Heart failure

Treatment of heart failure (NYHA class II-IV) in adult patients receiving standard therapy such as diuretics, digitalis and either angiotensin-converting enzyme (ACE) inhibitors or beta-blockers but not both; presence of all these standard therapies is not mandatory.

Diovan improves morbidity in these patients, primarily via reduction in hospitalization for heart failure. Diovan also slows the progression of heart failure, improves NYHA functional class, ejection fraction and signs and symptoms of heart failure and improves quality of life versus placebo (see section CLINICAL PHARMACOLOGY).

Post-myocardial infarction

Diovan is indicated to improve survival following myocardial infarction in clinically stable adult patients with signs, symptoms or radiological evidence of left ventricular failure and/or with left ventricular systolic dysfunction (see section CLINICAL PHARMACOLOGY).

Hypertensive adult patients with Impaired Glucose Tolerance at cardiovascular risk

Diovan is indicated in addition to lifestyle modifications to delay the progression to type 2 diabetes in hypertensive adult patients with impaired glucose tolerance at cardiovascular risk (see section CLINICAL PHARMACOLOGY)

DOSAGE AND ADMINISTRATION

Dosage

Adult population

Hypertension

The recommended dose of Diovan is 80 mg or 160 mg film-coated tablet 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 film-coated tablet, or a diuretic may be added.

Diovan may also be administered with other antihypertensive agents.

Heart failure

The recommended starting dose of Diovan is 40 mg film-coated tablet 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.

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, valsartan therapy should be titrated to 40 mg, 80 mg, and 160 mg film-coated tablet twice daily over the next few weeks. The starting dose is provided by the 40 mg divisible tablet.

The target maximum 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.

Valsartan 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.

Hypertensive adult patients with Impaired Glucose Tolerance at cardiovascular risk

The recommended starting dose of Diovan is 80 or 160 mg film-coated tablet once daily. For those patients starting on 80 mg, up-titration to 160 mg once daily should be done, as tolerated by the patient. If hypertension remains uncontrolled, please refer to section DOSAGE AND ADMINISTRATION, Hypertension.

NOTE for all indications: No dosage adjustment is required for patients with renal impairment or for patients with hepatic insufficiency of non-biliary origin and without cholestasis.

Special populations

Pediatric population (Pediatric Hypertension)

Children and adolescents 6-18 years of age

Film-coated tablet

The initial dose is a 40 mg tablet once daily for children and adolescents below 35 kg of weight and 80 mg once daily for those weighing 35 kg or more. The dose should be adjusted based on blood pressure response. For maximum doses studied in clinical trials please refer to the table below.

Doses higher than those listed have not been studied and are therefore not recommended.

	Weight	Maximum Dose studied in clinical trials	
	≥ 18 kg to <35 kg	80 mg	
	≥ 35 kg to < 80 kg	160 mg	
	≥ 80 kg to ≤ 160 kg	320 mg	

Oral Solution

For children and adolescents who are unable to swallow tablets, the use of the Diovan oral solution is recommended. The systemic exposure and peak plasma concentration of valsartan is about 1.7-fold and 2.2-fold higher with the oral solution compared to the tablets.

The initial dose for the Diovan oral solution is 20 mg (corresponding to approx.7 mL of the solution) once daily for children and adolescents below 35 kg of weight and 40 mg (corresponding to approx.13 mL of the solution) once daily for those weighing 35 kg or more. The dose should be adjusted based on blood pressure response up to a maximum dose of 40 mg valsartan once daily (corresponding to approx. 13 mL of the solution) for children and adolescents with body weight below 35 kg and 80 mg valsartan (corresponding to 27 mL of the solution) for children and adolescents with body weight of 35 kg or more.

Switching between Diovan tablets and Diovan oral solution

It is not recommended to switch between Diovan tablets and Diovan oral solution unless clinically required.

- If switching from Diovan tablets to Diovan oral solution is considered essential on clinical grounds, the valsartan dose should be adjusted as described in the table below and blood pressure should be carefully monitored. The dose should be titrated based on blood pressure response and tolerability.

Tablets	Solution	
Valsartan dose	Valsartan dose to provide when switching	Volume to take
40 mg	20 mg	7 mL
80 mg	40 mg	13 mL
160 mg	80 mg	27 mL
320 mg	Due to the high volume of solution that would be necessary, the use of the solution is not recommended	Not applicable

- If switching from Diovan oral solution to Diovan tablets is considered clinically essential, initially the same dose in milligrams should be given. Subsequently, frequent blood pressure monitoring should be performed taking into account potential under-dosing and the dose should be titrated further based on blood pressure response and tolerability.

Children less than 6 years of age

Available data are described in sections ADVERSE DRUG REACTIONS, CLINICAL PHARMACOLOGY and CLINICAL STUDIES. However safety and efficacy of Diovan in children less than 6 years of age have not been established.

Pediatric heart failure and recent myocardial infarction

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.

Method of administration

Film-coated tablets: Diovan may be taken independently of a meal and should be administered with water.

Oral solution: Diovan may be taken independently of a meal.

CONTRAINDICATIONS

Known hypersensitivity to valsartan or to any of the excipients of Diovan.

Pregnancy (see section WOMEN OF CHILD-BEARING POTENTIAL, PREGNANCY, BREAST-FEEDING AND FERTILITY).

Concomitant use of angiotensin receptor antagonists (ARBs) - including Diovan - or of angiotensin-converting-enzyme inhibitors (ACEIs) with aliskiren in patients with Type 2 diabetes (see section INTERACTIONS, subsection dual blockade of the RAS).

WARNINGS AND PRECAUTIONS

Patients with sodium- and/or volume-depletion

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.

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

Patients with 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 hemodynamics, serum creatinine, or blood urea nitrogen (BUN). However, since other drugs that affect the renin-angiotensin-aldosterone system (RAAS) 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.

Patients with impaired renal function

No dosage adjustment is required for patients with renal impairment. However, no data is available for severe cases (creatinine clearance <10 mL/min.), and caution is therefore advised.

The use of ARBs - including Diovan - or of ACEIs with aliskiren should be avoided in patients with severe renal impairment (GFR < 30 mL/min) (see section INTERACTIONS, subsection dual blockade of the RAS).

Patients with hepatic impairment

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

Patients with heart failure / post-myocardial infarction

Use of Diovan in patients with heart failure or post-myocardial infarction 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 DOSAGE AND ADMINISTRATION).

As a consequence of the inhibition of the 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 azotemia and (rarely) with acute renal failure and/or death. Evaluation of patients with heart failure or post-myocardial infarction should always include assessment of renal function.

In patients with heart failure, caution should be observed with the triple combination of an ACE inhibitor, a beta blocker and valsartan (see section CLINICAL PHARMACOLOGY).

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 System (RAS)

Caution is required while co-administering ARBs, including Diovan, with other agents blocking the RAS such as ACEIs or aliskiren (see section INTERACTIONS, subsection dual blockade of the RAS).

Pediatric population

Patients with impaired renal function

Use in pediatric patients with a glomerular filtration rate <30 mL/min/1.73 m² and pediatric patients undergoing dialysis has not been studied, therefore valsartan is not recommended in these patients. No dose adjustment is required for pediatric patients with a glomerular filtration rate >30 mL/min/1.73 m² (see section CLINICAL PHARMACOLOGY - pharmacokinetics). 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.

Patients with impaired hepatic function

As in adults, particular caution should be exercised when administering valsartan to pediatric patients with biliary obstructive disorders (see section CLINICAL PHARMACOLOGY-pharmacokinetics). There is limited clinical experience with Diovan in pediatric patients with mild to moderate hepatic impairment.

Special excipients (Diovan oral solution)

Diovan oral solution contains 0.3 g sucrose per milliliter. This should be taken into account in patients with diabetes mellitus.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take Diovan oral solution as it contains sucrose.

Diovan oral solution contains methyl parahydroxybenzoate which may cause allergic reactions (possibly delayed).

Diovan oral solution contains poloxamer (188) which may cause softened stools

Change of pharmaceutical form

Diovan oral solution is not bioequivalent to the tablet formulation and patients should not be switched unless clinically essential. For dosing recommendations in this case, see section DOSAGE AND ADMINISTRATION.

ADVERSE DRUG REACTIONS

In controlled clinical studies in adult patients with hypertension, the overall incidence of adverse 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 in table 1 according to system organ class.

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 ($< 1/10,000$), including isolated reports. Within each frequency grouping, adverse 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.

Table 1 Adverse drug reactions in Hypertension

Blood and lymphatic system disorders	
Not known	Hemoglobin decreased, Hematocrit decreased, Neutropenia, Thrombocytopenia
Immune system disorders	
Not known	Hypersensitivity including serum sickness
Metabolism and nutrition disorders	

Not known	Blood potassium increased
Ear and labyrinth system 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	Liver function test abnormal including blood 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, Blood creatinine increased
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, edema, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection, viral infections.

Hypertensive adult patients with Impaired Glucose Tolerance at cardiovascular risk

In the NAVIGATOR study, adverse events with Diovan were similar to those reported previously for patients with hypertension.

Pediatric population (Hypertension)

The antihypertensive effect of valsartan has been evaluated in two randomized, double-blind clinical studies in 561 pediatric patients from 6 to 18 years of age. No relevant differences in terms of type, frequency and severity of adverse reactions were identified between the safety profile for pediatric patients aged 6 to 18 years and that previously reported for adult patients.

Neurocognitive and developmental assessment of pediatric patients aged 6 to 16 years of age revealed no overall clinically relevant adverse impact after treatment with Diovan for up to one year.

In a double-blind randomized study in 90 children aged 1 to 6 years, which was followed by a one-year open-label extension, two deaths and isolated cases of marked liver transaminases elevations were observed. In a second study in which 75 children aged 1 to 6 years were randomized, no deaths and one case of marked liver transaminase elevations occurred during a one year open-label

extension. These cases occurred in a population who had significant comorbidities. A causal relationship to Diovan has not been established.

Hyperkalemia has been observed in children and adolescents aged 6 to 18 years with underlying chronic kidney disease.

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 patients underlying disease. ADRs that occurred in heart failure and/or post-myocardial infarction patients are listed below in table 2:

Table 2 Adverse drug reactions in heart failure and/or post-myocardial infarction

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	Blood potassium increased
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
Not known	Vasculitis
Respiratory, thoracic and mediastinal disorders	
Uncommon	Cough
Gastrointestinal disorders	
Uncommon	Nausea, Diarrhea
Hepato-biliary disorders	
Not known	Liver function test abnormal
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, Blood creatinine increased

Not known	Blood Urea 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, edema, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection, viral infections.

INTERACTIONS

Dual blockade of the Renin-Angiotensin- System (RAS) with ARBs, ACEIs, or aliskiren: The concomitant use of ARBs, including Diovan, with other agents acting on the RAS is associated with an increased incidence of hypotension, hyperkalemia, 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 agents that affect the RAS (see section WARNINGS AND PRECAUTIONS).

The concomitant use of ARBs - including Diovan - or of ACEIs with aliskiren, should be avoided in patients with severe renal impairment (GFR < 30 ml/min) (see section WARNINGS AND PRECAUTIONS).

The concomitant use of ARBs - including Diovan - or ACEIs with aliskiren is contraindicated in patients with Type 2 diabetes (see section CONTRAINDICATIONS).

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

Non-Steroidal Anti-Inflammatory Agents (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 patients who are elderly, volume-depleted (including those on diuretic therapy), or have 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 during concomitant administration of lithium with ACE inhibitors or angiotensin II receptor antagonists, including Diovan. Therefore, careful monitoring of serum lithium levels is recommended during concomitant use. If a diuretic is also used, the risk of lithium toxicity may presumably be increased further with Diovan.

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 (rifampin, ciclosporin) or efflux transporter (ritonavir) may increase the systemic exposure to valsartan.

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

As valsartan is not metabolized 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.

Pediatric population

In hypertension in children and adolescents, where underlying renal abnormalities are common, caution is recommended with the concomitant use of valsartan and other substances that inhibit the renin angiotensin aldosterone system which may increase serum potassium. Renal function and serum potassium should be closely monitored in these patients.

WOMAN OF CHILD-BEARING POTENTIAL (WOCBP), PREGNANCY, BREAST-FEEDING AND FERTILITY

Woman of child-bearing potential

As for any drug that also acts directly on the RAAS, Diovan should not be used in women planning to become pregnant. Healthcare professionals prescribing any agents acting on the RAAS should counsel women of childbearing potential about the potential risk of these agents during pregnancy.

Pregnancy

As for any drug that also acts directly on the RAAS, Diovan must not be used during pregnancy (see section CONTRAINDICATIONS). Due to the mechanism of action of angiotensin II antagonists, a risk for the fetus cannot be excluded. *In utero* exposure to ACE inhibitors (a specific class of drugs acting on the RAAS) during the second and third trimesters has been reported to cause injury and death to the developing fetus. In addition, in retrospective data, first trimester use of ACE inhibitors has been associated with a potential risk of birth defects. There have been reports of spontaneous abortion, oligohydramnios and new born renal dysfunction, when pregnant women have inadvertently taken valsartan. If pregnancy is detected during therapy, Diovan should be discontinued as soon as possible (see section NON-CLINICAL SAFETY DATA).

Breast-feeding

It is not known whether valsartan is excreted in human milk. Since valsartan was excreted in the milk of lactating rats, it is not advisable to use Diovan in breast-feeding mothers.

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 (see section NON-CLINICAL SAFETY DATA).

OVERDOSAGE

Overdosage 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 i.v. infusion of normal saline solution.

Valsartan is unlikely to be removed by hemodialysis.

CLINICAL PHARMACOLOGY

Pharmacodynamics (PD)

The active hormone of the RAAS is angiotensin II, which is formed from angiotensin I through ACE. Angiotensin II binds to specific receptors located in the cell membranes of various tissues. It has a wide variety of physiological effects, including in particular both direct and indirect involvement in the regulation of blood pressure. As a potent vasoconstrictor, angiotensin II exerts a direct pressor response. In addition, it promotes sodium retention and stimulation of aldosterone secretion.

Diovan (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 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 cough. In clinical trials where valsartan was compared with an ACE inhibitor, the incidence of dry cough was significantly ($P < 0.05$) lower in patients treated with valsartan than in those treated with an ACE inhibitor (2.6% versus 7.9% respectively). In a clinical trial of patients with a history of dry cough during ACE inhibitor therapy, 19.5% of trial subjects receiving valsartan and 19.0% of those receiving a thiazide diuretic experienced cough compared to 68.5% of those treated with an ACE inhibitor ($P < 0.05$). Valsartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Pharmacokinetics (PK)

Absorption

Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2–4 hours. Mean absolute bioavailability 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 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

Steady-state volume of distribution of valsartan after intravenous administration is about 17 liters, indicating that valsartan is not distributed into tissues extensively. Valsartan is highly bound to serum proteins (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 ($t_{1/2\alpha} < 1$ h and $t_{1/2\beta}$ about 9 h). Valsartan is primarily eliminated in feces (about 83% of dose) and urine (about 13% of dose), mainly as unchanged drug. Following intravenous administration, plasma clearance of valsartan is about 2 L/h and its renal clearance is 0.62 L/h (about 30% of total clearance). The half-life of valsartan is 6 hours.

The pharmacokinetics of valsartan are 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 were observed to be 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 is approximately 4.5 L/h. Age does not affect the apparent clearance in heart failure patients.

Special populations

Geriatric patients (aged 65 years or above) A somewhat higher systemic exposure to valsartan was observed in some elderly subjects compared to young subjects; however, this has not been shown to have any clinical significance.

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. 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, as expected, 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 approximately double in patients with biliary cirrhosis or biliary obstruction (see section WARNINGS AND PRECAUTIONS).

Pediatric population

In a study of 26 pediatric 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 (liters/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 WARNINGS AND PRECAUTIONS in pediatric patients).

CLINICAL STUDIES

Hypertension

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 maximum reduction in blood pressure with any dose is generally attained within 2-4 weeks and is sustained 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 multiple dose studies in hypertensive patients valsartan had no notable effects on total cholesterol, fasting triglycerides, fasting serum glucose, or uric acid.

Heart failure

Hemodynamics and neurohormones. Hemodynamics and plasma neurohormones were measured in NYHA class II-IV heart failure patients with pulmonary capillary wedge pressure >15 mmHg in 2 short-term, chronic therapy studies. In one study, which included patients chronically treated with ACE inhibitors, single and multiple doses of valsartan given in combination with an ACE inhibitor improved hemodynamics including pulmonary capillary wedge pressure (PCWP), pulmonary artery diastolic pressure (PAD) and systolic blood pressure (SBP). Reductions were observed in plasma aldosterone (PA) and plasma noradrenalin (PNE) levels after 28 days of treatment. In the second study, which included only patients untreated with ACE inhibitors for at least 6 months prior to enrolment, valsartan significantly improved PCWP, systemic vascular resistance (SVR), cardiac output (CO) and SBP after 28 days of treatment. In the long-term Val-HeFT study, plasma noradrenalin and brain natriuretic peptide (BNP) were significantly reduced from baseline in the valsartan group compared to placebo.

Morbidity and mortality. Val-HeFT was a randomized, controlled, multinational clinical trial of valsartan compared with placebo on morbidity and mortality in 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. The study enrolled 5010 patients in 16 countries who were randomized to receive either valsartan or placebo in addition to all other appropriate

therapy including 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 2 primary endpoints: all cause mortality (time to death) 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 in the valsartan and placebo groups. Morbidity was significantly reduced by 13.2% with valsartan compared with placebo. The primary benefit was a 27.5% reduction in risk for time to first heart failure hospitalization. The benefits were greatest in patients not receiving either an ACE inhibitor or a beta blocker. However, risk reductions favoring placebo were observed for those patients treated with the triple combination of a beta blocker, an ACE inhibitor and valsartan. Further studies such as VALIANT (see section on Post-myocardial infarction), where mortality was not increased in these patients, have reduced the concerns regarding the triple combination.

Exercise tolerance and capacity. The effects of valsartan in addition to usual heart failure therapy on exercise tolerance using the Modified Naughton Protocol were measured in NYHA class II-IV heart failure patients with left ventricular dysfunction (LVEF $\leq 40\%$). Increased exercise time from baseline was observed for all treatment groups. Greater mean increases from baseline in exercise time were observed for the valsartan groups compared to the placebo group, although statistical significance was not achieved. The greatest improvements were observed in the subgroup of patients not receiving ACE inhibitor therapy where mean changes in exercise time were two times greater for the valsartan groups compared to the placebo group. The effects of valsartan compared to enalapril on exercise capacity using the six minute walk test were determined in NYHA class II and III heart failure patients with left ventricular ejection fraction $\leq 45\%$ who had been receiving ACE inhibitor therapy for at least 3 months prior to study entry. Valsartan 80 mg to 160 mg once daily was at least as effective as enalapril 5 mg to 10 mg twice daily, with respect to exercise capacity, as measured by the six minute walk test in patients previously stabilized on ACE inhibitors and directly switched to valsartan or enalapril.

NYHA class, Signs and symptoms, Quality of life, Ejection fraction. In Val-HeFT, valsartan treated patients showed significant improvement in NYHA class, and heart failure signs and symptoms, including dyspnoea, fatigue, edema and rales compared to placebo. Patients on 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 LVDD significantly reduced from baseline at endpoint compared to placebo.

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 (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 one of three treatment groups: valsartan (titrated from 20 mg twice daily to highest tolerated dose up to a maximum of 160 mg twice daily), the ACE inhibitor captopril (titrated from 6.25 mg three times daily to highest tolerated dose up to a maximum of 50 mg three times daily), or the combination

of valsartan plus captopril. In the combination group, the dose of valsartan was titrated from 20 mg twice daily to highest tolerated dose up to a maximum of 80 mg twice daily; the dose of captopril was the same as for monotherapy. The mean treatment duration was two years. The mean daily dose of Diovan in the monotherapy group was 217 mg. Baseline therapy included acetylsalicylic acid (91%), beta-blockers (70%), ACE inhibitors (40%), thrombolytics (35%), and statins (34%). The population studied was 69% male, 94% Caucasian, and 53% were 65 years of age or older. The primary endpoint was time to all-cause mortality.

Valsartan was at least 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. 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).

Since this was a trial with an active control (captopril), an additional analysis of all-cause mortality was performed to estimate how valsartan would have performed versus placebo. Using the results of the previous reference myocardial infarction trials – SAVE, AIRE, and TRACE – the estimated effect of valsartan preserved 99.6% of the effect of captopril (97.5% CI = 60–139%). Combining valsartan with captopril did not add further benefit over captopril alone. There was no difference in all-cause mortality based on age, gender, race, baseline therapies or underlying disease.

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 study drug treatment, mortality was higher in the group of patients not treated with a beta-blocker, suggesting that the known beta blocker benefit in this population was maintained in this trial. In addition, the treatment benefits of the combination of valsartan + captopril, valsartan monotherapy, and captopril monotherapy were maintained in patients treated with beta blockers.

Hypertensive adult patients with Impaired Glucose Tolerance at cardiovascular risk

The Nateglinide And Valsartan Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial was a multinational, double-blind, placebo-controlled, forced-titration 2x2 factorial design study in which 9,306 patients with impaired glucose tolerance at cardiovascular risk were randomized to placebo, valsartan (titrated from 80 mg once daily to 160 mg once daily, as tolerated), nateglinide (a D-phenylalanine derivative with insulinotropic activity) or nateglinide + valsartan, in addition to lifestyle modification. Patients were followed for a median of about 5 years for the development of diabetes. The population studied was 49% male, 43% 65 years or older and 83% Caucasian. The most commonly reported cardiovascular risk factors at baseline included hypertension (78%) and dyslipidemia (45%) with the majority of these patients receiving antihypertensive and lipid lowering therapy, respectively. Established cardiovascular disease was present in 24% of patients with the most common diagnoses being previous myocardial infarction (12%) and angina with documented multivessel coronary artery disease (9%). During the study, lipid lowering agents were used by 56% of patients and anti-thrombotic agents by 55% of patients.

There were three co-primary endpoints: 1) development of diabetes, 2) extended composite cardiovascular endpoint (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, arterial revascularization or hospitalization for

unstable angina), 3) core composite cardiovascular endpoint that excluded unstable angina and arterial revascularization.

There was a statistically significant 14% reduction in the risk of progression to diabetes in valsartan-treated patients also receiving lifestyle intervention measures. However, there was a neutral effect on the core and extended cardiovascular endpoints. These effects were consistent in the large subgroup of patients with hypertension and also across subgroups defined by age, gender, and race. The number of black patients was small and results in this subgroup should be viewed with caution.

There also was a significant reduction in risk of the development of micro albuminuria in valsartan-treated patients compared to non-valsartan treated patients [5.8% vs. 8.4%; HR 0.68; 95% CI (0.573, 0.800); $p < 0.0001$].

Pediatric population (Hypertension)

The antihypertensive effect of valsartan have been evaluated in four randomized, double-blind clinical studies in 561 pediatric patients from 6 to 18 years of age and 165 pediatric patients 1 to 6 years of age. Renal and urinary disorders, and obesity were the most common underlying medical conditions potentially contributing to hypertension in the children and adolescents enrolled in these studies.

Clinical experience in children and adolescents at or above 6 years of age

In a clinical study involving 261 hypertensive pediatric patients 6 to 16 years of age, patients who weighed < 35 kg received 10, 40 or 80 mg of valsartan tablets daily (low, medium and high doses), and patients who weighed ≥ 35 kg received 20, 80, and 160 mg of valsartan tablets daily (low, medium and high doses). At the end of 2 weeks, valsartan reduced both systolic and diastolic blood pressure in a dose-dependent manner. Overall, the three dose levels of valsartan (low, medium and high) significantly reduced systolic blood pressure by 8, 10, 12 mm Hg from the baseline, respectively. Patients were re-randomized to either continue receiving the same dose of valsartan or were switched to placebo. In patients who continued to receive the medium and high doses of valsartan, systolic blood pressure at trough was -4 and -7 mm Hg lower than patients who received the placebo treatment. In patients receiving the low dose of valsartan, systolic blood pressure at trough was similar to that of patients who received the placebo treatment. Overall, the dose-dependent antihypertensive effect of valsartan was consistent across all the demographic subgroups.

In another clinical study involving 300 hypertensive pediatric patients 6 to 18 years of age, eligible patients were randomized to receive valsartan or enalapril tablets for 12 weeks. Children weighing between ≥ 18 kg and < 35 kg received valsartan 80 mg or enalapril 10 mg; those between ≥ 35 kg and < 80 kg received valsartan 160 mg or enalapril 20 mg; those ≥ 80 kg received valsartan 320 mg or enalapril 40 mg. Reductions in systolic blood pressure were comparable in patients receiving valsartan (15 mmHg) and enalapril (14 mm Hg) (non-inferiority p -value < 0.0001). Consistent results were observed for diastolic blood pressure with reductions of 9.1 mmHg and 8.5 mmHg with valsartan and enalapril, respectively.

Clinical experience in children less than 6 years of age

Two clinical studies were conducted in patients aged 1 to 6 years with 90 and 75 patients, respectively. No children below the age of 1 year were enrolled in these studies. In the first study,

the efficacy of valsartan was confirmed compared to placebo but a dose-response could not be demonstrated. In the second study, higher doses of valsartan were associated with greater BP reductions, but the dose response trend did not achieve statistical significance and the treatment difference compared to placebo was not significant. Because of these inconsistencies, valsartan is not recommended in this age group (see section ADVERSE DRUG REACTIONS).

NON-CLINICAL 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, hemoglobin, hematocrit) and evidence of changes in renal hemodynamics (slightly raised blood urea nitrogen, 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 comparable doses, the changes were similar though more severe, particularly in the kidney where the changes developed to a nephropathy including raised blood urea nitrogen 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.

Reproductive toxicity

Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day. In embryofetal development studies (Segment II) in mice, rats and rabbits, fetotoxicity was observed in association with maternal toxicity in rats at valsartan doses of 600 mg/kg/day and in rabbits at doses of 10 mg/kg/day. In a peri- and postnatal development toxicity (Segment III) study, the offspring of rats given 600 mg/kg/day during the last trimester and during lactation showed a slightly reduced survival rate and a slight developmental delay (see section WOCBP, PREGNANCY, BREAST-FEEDING AND FERTILITY). The main preclinical safety findings are attributed to the pharmacological action of the compound, and have not been demonstrated to have any clinical significance.

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.

Pediatric 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 10-35% of the maximum recommended pediatric dose of approximately 4 mg/kg/day on systemic exposure basis) produced persistent, irreversible kidney damage. These 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 4-6 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.

INCOMPATIBILITIES

Not applicable.

STORAGE

See folding box.

Oral solution: Once opened, the bottle can be stored for up to 3 months at temperatures below 30°C.

Diovan should not be used after the date marked “EXP” on the pack.

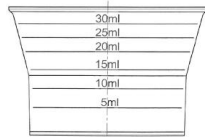
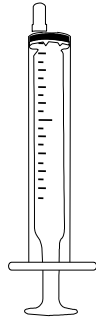
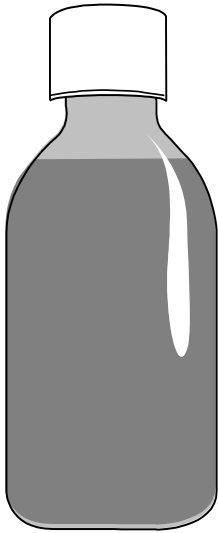
Diovan must be kept out of the reach and sight of children.

INFORMATION FOR PATIENTS

Instructions for using the oral syringe and the dosing cup

Please read these instructions carefully before taking the medicine. This will help you to use the oral syringe and the dosing cup correctly.

What you will be using



A press in bottle adapter:

- that you insert into the neck of the bottle.
- Once you have inserted it, do not remove it.

A bottle containing the medicine:

- that has a child-resistant screw cap.
- Always screw the cap back on after use.

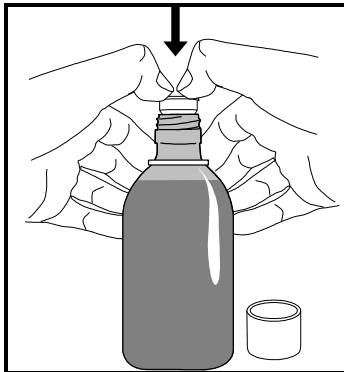
An oral dosing syringe:

- that consists of a clear plastic tube with a plunger inside.
- The oral syringe fits into the bottle adapter and is used to measure out the required amount of medicine from the bottle. Use a new bottle adapter and oral dosing syringe each time you start a new bottle of medicine.

A dosing cup:

- that can be used if the prescribed dose requires filling the syringe several times.
- Always put the dosing cup back onto the cap after use and cleaning.

Fitting the press in bottle adapter into a new bottle of medicine

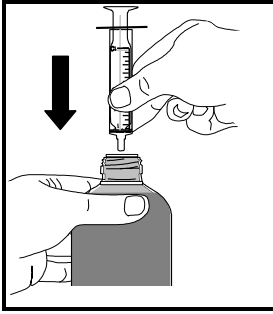


1. Remove the cap from the bottle by pushing it down **firmly** and turning it anti-clockwise (as shown on the top of the cap).
2. Holding the open bottle upright on a table, push the bottle adapter **firmly** into the neck of the bottle as far as it will go.

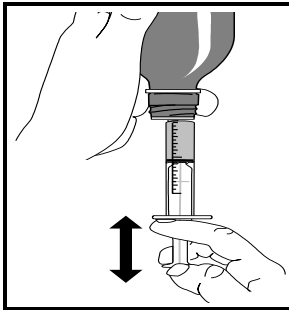
Note: You may not be able to push the bottle adapter down fully but this does not matter as it will be forced into the bottle when you screw the cap back on.

3. Screw the cap back on the bottle.

Preparing a dose of medicine



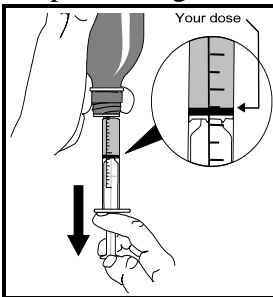
4. Remove the cap from the bottle by pushing it down **firmly** and turning it anti-clockwise (as shown on the top of the cap).
5. Check that the plunger is pushed fully into the oral syringe.
6. Keeping the bottle upright, insert the oral syringe **firmly** into the bottle adapter.



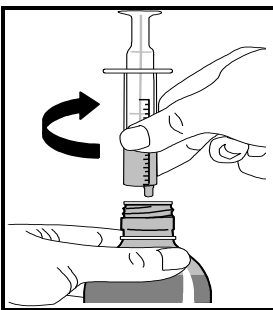
7. Holding the oral syringe in place, carefully turn the bottle and oral syringe upside down.
8. Before you measure your dose you need to get rid of any large bubbles that may be trapped in the oral syringe. To do this:
 - slowly pull the plunger all the way out so that the oral syringe fills with medicine.
 - then, push the plunger all the way back in so that it is empty again.

Measuring a dose of medicine

Note: The total amount of solution that can be measured into the oral syringe is 5 mL. Depending on the prescribed dose, it may be necessary to repeat steps 10 to 16 several times. For example, if the prescribed dose is 13 mL, it will be necessary to measure out the solution in three separate stages: 5 mL + 5 mL + 3 mL.

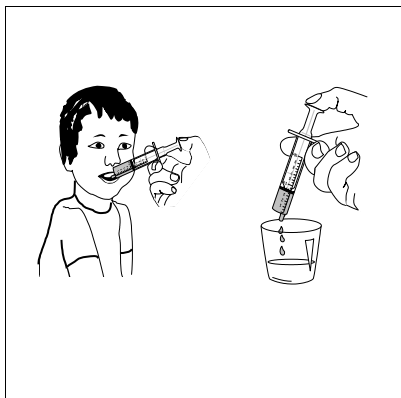


9. Find the marker on the oral syringe that corresponds to the required amount of medicine.
10. Slowly pull the plunger out until the top edge of the black ring inside is exactly level with the marker.
11. Carefully turn the bottle and oral syringe back upright.



12. Remove the oral syringe from the bottle adapter by gently twisting it out.

Taking the medicine



13. Sit upright.
14. Put the end of the oral syringe into the mouth.
15. Slowly push the plunger in and swallow the medicine directly from the oral syringe.
16. If the prescribed dose requires filling the syringe several times, **you can empty the measured doses of medicine from the syringe into the dosing cup** and then check the total volume of solution.
17. Drink the entire solution right away.
18. Replace the child-resistant screw cap after use
19. **To clean the oral syringe:**
 - Wipe the outside of the oral syringe with a clean, dry tissue.
 - Do this after each time that you use the oral syringe.
20. **To clean the cup:**
 - Rinse the cup with clean water.
 - Dry the cup with a clean tissue and place it back over the cap of the bottle.

Novartis Pharma AG, Basel, Switzerland