PROFESSIONAL INFORMATION

SCHEDULING STATUS S3

PROPRIETARY NAMES (AND DOSAGE FORM)

Dafiro® 5/160 mg film-coated tablet

Dafiro® 10/160 mg film-coated tablet

Dafiro® 5/320 mg film-coated tablet

Dafiro® 10/320 mg film-coated tablet

Sugar-free.

COMPOSITION

Active ingredient:

DAFIRO 5/160 mg:	Each film-coated tablet contains 6,94 mg amlodipine besylate (equivalent to 5 mg amlodipine base) and 160 mg valsartan.
DAFIRO 10/160 mg:	Each film-coated tablet contains 13,87 mg amlodipine besylate (equivalent to 10 mg amlodipine base) and 160 mg valsartan.
DAFIRO 5/320 mg:	Each film-coated tablet contains 6,94 mg amlodipine besylate (equivalent to 5 mg amlodipine base) and 320 mg valsartan.
DAFIRO 10/320 mg:	Each film-coated tablet contains 13,87 mg amlodipine besylate (equivalent to 10 mg amlodipine base) and 320 mg valsartan.

List of excipients:

Dafiro 5/160 mg: Microcrystalline cellulose; crospovidone; colloidal silicon dioxide, anhydrous; magnesium stearate; hypromellose; polyethylene glycol 4000; talc; titanium dioxide (E171); iron oxide, yellow (E172).

Dafiro 10/160 mg: Microcrystalline cellulose; crospovidone; colloidal silicon dioxide, anhydrous, magnesium stearate; hypromellose; polyethylene glycol 4000; talc; titanium dioxide (E171); iron oxide, yellow (E172); iron oxide, red (E172).

Dafiro 5/320 mg: Microcrystalline cellulose; sodium starch glycolate, crospovidone; colloidal silicon dioxide, anhydrous; magnesium stearate; hypromellose, polyethylene glycol 4000, talc, titanium dioxide (E171), iron oxide, yellow (E172), iron oxide, red (E172).

Dafiro 10/320 mg: Microcrystalline cellulose; sodium starch glycolate, crospovidone; colloidal silicon dioxide, anhydrous; magnesium stearate; hypromellose, polyethylene glycol 4000, talc, titanium dioxide (E171), iron oxide, yellow (E172).

PHARMACOLOGICAL CLASSIFICATION

A 7.1.3 Vascular medicines - other hypotensives

PHARMACOLOGICAL ACTION

Pharmacodynamic Properties:

Dafiro combines two antihypertensive compounds with separate mechanisms of action: amlodipine belongs to the calcium antagonist class and valsartan to the angiotensin II (Ang II) antagonist class of medicines.

Amlodipine:

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

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

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

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

Amlodipine has minimal effect on sinoatrial nodal function or atrioventricular conduction.

Valsartan:

Valsartan is an orally active, and specific angiotensin 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 angiotensin 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 (about 20,000 fold) greater affinity for the AT_1 receptor than for the AT_2 receptor.

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

Valsartan has been demonstrated to significantly reduce hospitalisations in patients with chronic heart failure (NYHA class II-IV). The benefits were greatest in patients not receiving either an ACE inhibitor or a beta blocker. Valsartan has also been shown to reduce cardiovascular mortality in clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction.

Valsartan/Amlodipine:
The antihypertensive effect of a single dose of Dafiro persists for 24 hours. Age, gender and race did not influence the response to Dafiro.

PHARMACOKINETIC PROPERTIES

Linearity:
Valsartan and amlodipine exhibit linear pharmacokinetics.

Amlodipine:
Absorption: After oral administration of therapeutic doses of amlodipine alone, peak plasma concentrations of amlodipine are reached in 6-12 hours. Absolute bioavailability has been calculated as between 64 % and 80 %. Amlodipine bioavailability is unaffected by food ingestion. (See absorption of combination tablet below).

Distribution: Volume of distribution is approximately 21 *l*/kg. *In vitro* studies with amlodipine have shown that approximately 97,5 % of circulating compound is bound to plasma proteins in hypertensive patients.

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

Excretion: Amlodipine elimination from plasma is biphasic with a terminal elimination half-life of approximately 30 to 50 hours. Steady-state plasma levels are reached after continuous administration

for 7-8 days. Ten percent of original amlodipine and 60 % of amlodipine metabolites are excreted in urine.

Valsartan:

Absorption: Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2-4 hours. Mean absolute bioavailability is 23 %. Valsartan shows multi-exponential decay kinetics ($t_{1/2}$ α <1 h and $t_{1/2}$ ß about 9 h). Food decreases the exposure (as measured by AUC) to valsartan by about 40 % and peak plasma concentration (Cmax) by about 50 %, although from about 8 h post dosing plasma valsartan concentrations are similar for the fed and fasted 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. (See absorption of combination tablet below).

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

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

Excretion: Valsartan is primarily eliminated unchanged in faeces (about 83 % of dose) and urine (about 13 % of dose) mainly as unchanged compound. Following intravenous administration, plasma clearance of valsartan is about 2 L/h and its renal clearance is 0,62L/h (about 30 % of total clearance). The half-life of valsartan is 6 hours.

Valsartan/Amlodipine:

Following oral administration of Dafiro peak plasma concentrations of valsartan and amlodipine are reached in 3 and 6-8 hours, respectively. The rate and extent of absorption of Dafiro are equivalent to the bioavailability of valsartan and amlodipine when administered as individual tablets. (See absorption of individual tablets above).

Special populations:

Paediatric:

No pharmacokinetic data are available in the paediatric population.

Elderly:

Systemic exposure to valsartan is slightly elevated in the elderly as compared to the young, but this has not been shown to have any clinical significance. Since the two components are equally well tolerated in younger and elderly patients, normal dose regimens are recommended (see Dosage and Directions for use).

Renal impairment:

The pharmacokinetics of amlodipine is not significantly influenced by renal impairment. There is no apparent correlation between renal function (measured by creatinine clearance) and exposure (measured by AUC) to valsartan in patients with different degrees of renal impairment. Patients with mild to moderate renal impairment may therefore receive the usual initial dose (See Dosage and Directions for use and Side-Effects and Special Precautions)

Hepatic impairment:

Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase in AUC of approximately 40-60 % in AUC. On average, in patients with mild to moderate chronic liver disease exposure (measured by AUC values) to valsartan is twice thatfound in healthy volunteers (matched by age, sex and weight). Care should be exercised in patients with liver disease (See Dosage and Directions for use and Side-Effects and Special Precautions).

INDICATIONS

Treatment of mild to moderate essential hypertension in patients whose blood pressure is normalized with the individual components in the same doses as the proposed fixed dose combination of Dafiro.

CONTRA-INDICATIONS

- Sensitivity to any of the components of Dafiro.
- A history of angioedema related to previous therapy with ACE inhibitors or angiotensin receptor blockers (ARBs): These patients must never again be giventhese medicines.
- Hereditary or idiopathic angioedema
- Hypertrophic obstructive cardiomyopathy (HOCM)
- Aortic stenosis
- Severe renal function impairment (creatinine clearance less than 30 ml/min)
- Bilateral renal artery stenosis.
- Renal artery stenosis in patients with a single kidney
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride.
- Porphyria.
- Lithium therapy: Concomitant administration with Dafiro may lead to toxic blood concentrations of lithium.
- Pregnancy and lactation (see Pregnancy and lactation).

WARNINGS

Renal Impairment:

Amlodipine is extensively metabolised to inactive metabolites with 10 % excreted unchanged in the urine. Changes in amlodipine plasma concentrations are not correlated with mild renal impairment.

Dafiro may be used in such patients at normal doses. In patients with severe renal impairment, Dafiro containing reduced amlodipine dosages (5 mg) may need to be administered in these patients. Amlodipine is not dialysable.

Hepatic Impairment:

Amlodipine half-life is prolonged in patients with impaired liver function. Dafiro containing lower amlodipine dosages (5 mg) should therefore be administered in these patients.

Children:

Safety and effectiveness of Dafiro in children has not been established.

INTERACTIONS

Amlodipine:

In monotherapy, amlodipine has been safely administered with thiazide diuretics, beta- blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, *digoxin, warfarin, atorvastatin, sildenafil, Maalox® (Aluminium hydroxide gel, Magnesium hydroxide and Simeticone), cimetidine*, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycaemic medicines.

Studies have indicated that the co-administration of monotherapy amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in renal clearance in normal volunteers, and that co-administration of cimetidine did not alter the pharmacokinetics of amlodipine.

In vitro data from studies with human plasma indicate that monotherapy amlodipine has no effect on protein binding of the medicines tested (digoxin, phenytoin, warfarin, or indomethacin).

In healthy male volunteers, the co-administration of monotherapy amlodipine does not significantly alter the effect of warfarin on prothrombin response time.

Pharmacokinetics studies with cyclosporin have demonstrated that monotherapy amlodipine does not significantly alter the pharmacokinetics of cyclosporin.

Valsartan:

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

Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other medicines that may increase potassium levels (heparin, etc.) requires caution and frequent monitoring of potassium levels (see Contra-indications).

PREGNANCY AND LACTATION

Pregnancy:

Safety of ARB's in pregnancy has not been established.

ACE-inhibitors pass through the placenta and can be presumed to cause disturbance in foetal blood

pressure regulatory mechanisms. Oligohydramnios as well as hypotension, oliguria and anuria in newborns, have been reported after administration of ACE-inhibitors in the second and third trimester.
Safety in pregnancy and lactation has not been established

Dafiro acts directly on the renin-angiotensin system therefore a risk to the foetus cannot be excluded. When pregnancy is detected during therapy, Dafiro must be discontinued as soon as possible. Dafiro must not be used during pregnancy as teratogenicity has been shown with valsartan in experimental animals (see Contra-indications).

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

Lactation:

It is not known whether valsartan and/or amlodipine are excreted in human milk. Valsartan was excreted in the milk of lactating rats. Dafiro is contra-indicated for women who are breast-feeding (see Contra-indications).

DOSAGE AND DIRECTIONS FOR USE

Patients receiving valsartan and amlodipine from separate tablets may be switched to Dafiro containing the same component doses.
The recommended dose is one tablet per day (the 5 strengths are listed under Composition). It is recommended to take Dafiro with some water.

In Elderly:

Normal dosage regimens are recommended

Children and adolescents:

Dafiro is not recommended for use in patients aged below 18 years due to a lack of data on safety and efficacy (see Warnings).

Renal impairment:

No dosage adjustment is required for patients with mild to moderate renal impairment. In patients with severe renal impairment dosages may need to be reduced (see Warnings).

Hepatic impairment:

Caution should be exercised when administering Dafiro to patients with hepatic impairment or biliary obstructive disorders (see Side-effects and Special Precautions).

SIDE-EFFECTS AND SPECIAL PRECAUTIONS

Side-effects:

The safety of Dafiro has been evaluated in five controlled clinical studies with 5 175 patients, 2 613 of whom received valsartan in combination with amlodipine at variable dosage combinations. Adverse reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: 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), including isolated reports.

Table 1:

Infections and infestations	
Common:	Nasopharyngitis, influenza
Immune system disorders	
Rare:	Hypersensitivity
Eye disorders	
Rare	Visual disturbance
Psychiatric disorders	
Rare:	Anxiety
Nervous system disorders	
Common:	Headache
Uncommon:	Dizziness, somnolence, dizziness postural, paraesthesia
Ear and labyrinth disorders	
Uncommon:	Vertigo
Rare:	Tinnitus
Cardiac disorders	
Uncommon:	Tachycardia, palpitations
Rare:	Syncope
Vascular disorders	
Uncommon:	Orthostatic hypotension
Rare:	Hypotension
Respiratory, thoracic and mediastinal disorders	
Uncommon:	Cough, pharyngolaryngeal pain
Gastrointestinal disorders	
Uncommon:	Diarrhoea, nausea, vomiting, abdominal pain, constipation, dry mouth
Skin and subcutaneous tissue disorders	
Uncommon:	Rash, erythema
Rare:	Hyperhidrosis, exanthema, pruritus
Musculoskeletal and connective tissue disorders	
Uncommon:	Joint swelling, back pain, arthralgia
Rare:	Muscle spasm, sensation of heaviness

Renal and urinary disorders	
Rare:	Pollakiuria, polyuria
Reproductive system and breast disorders	
Rare:	Erectile dysfunction
General disorders and administration site conditions	
Common:	Oedema, pitting oedema, facial oedema, oedema peripheral, fatigue, flushing, asthenia, hot flushes

Additional information on the combination:
In double-blind, active- or placebo-controlled completed clinical trials, the incidence of peripheral oedema was statistically lower in patients treated with the combination (5,8 %) than in patients treated with amlodipine monotherapy (9 %).

Additional information on individual components:
Adverse reactions previously reported with one of the individual components may occur with Dafiro even if not observed in clinical trials.

Amlodipine:
Other additional adverse experiences reported in clinical trials with amlodipine monotherapy, irrespective of their causal association with the study medicine, were as follows:
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 2:

Blood and lymphatic system disorders:	
Uncommon:	Leucopenia, thrombocytopenia,
Metabolism and nutrition disorders:	
Uncommon:	Hyperglycaemia
Eye disorders:	
Uncommon:	Visual Disturbances
Nervous system disorders:	
Common:	Headache, somnolence, dizziness
Uncommon:	Peripheral neuropathy
Cardiac disorders:	
Common:	Palpitations
Uncommon:	Syncope

Hepato-biliary disorders:	
Uncommon:	Pancreatitis, hepatitis
Vascular disorders:	
Uncommon:	Angioedema, vasculitis
Respiratory, thoracic and mediastinal disorders:	
Uncommon:	Dyspnoea, rhinitis
Gastrointestinal disorders:	
Common:	Nausea, vomiting, abdominal pain
Uncommon:	Altered bowel habits, dyspepsia, gastritis, gingival hyperplasia, dry mouth
Skin and subcutaneous tissue disorders:	
Uncommon:	Alopecia, increased sweating, pruritus, rash, erythema multiforme
Musculoskeletal and connective tissue disorders:	
Uncommon:	Myalgia, arthralgia, back pain, muscle cramps
Renal and urinary disorders:	
Uncommon:	Increased urinary frequency
General disorders and administration site conditions:	
Common:	Oedema, fatigue, flushing
Uncommon:	Malaise, mood changes, depression, asthenia
Reproductive system and breast disorders:	
Uncommon:	Gynaecomastia, impotence

In a long-term, placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure of non-ischaemic aetiology, amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

Valsartan:

Other additional adverse experiences reported in clinical trials with valsartan monotherapy in the indication hypertension, irrespective of their causal association with the study medicine, were as follows:

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 3*:*

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:
Valsartan may be associated with decreases in haemoglobin and haematocrit.
Neutropenia was observed in 1,9 % of patients treated with valsartan versus 1,6 % of patients treated with an ACE inhibitor.

Hypertensive patients:
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 valsartan 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 valsartan therapy.

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

Heart failure patients:
In heart failure patients, greater than 50 % increases in creatinine were observed in 3,9 % of valsartan-treated patients compared to 0,9 % of placebo-treated patients. In post-myocardial infarction patients, doubling of serum creatinine was observed in 4,2% of valsartan-treated patients and 3,4 % of captopril-treated patients.

In heart failure patients, greater than 20 % increases in serum potassium were observed in 10 % of valsartan-treated patients compared to 5,1 % of placebo-treated patients.

In heart failure patients, greater than 50 % increases in blood urea were observed in 16,6 % of valsartan-treated patients compared to 6,3 % of placebo-treated patients.

Special precautions:
Sodium- and/or volume depleted patients:

Excessive hypotension was seen in 0,4 % of patients with uncomplicated hypertension treated with Dafiro in placebo-controlled studies. In patients with an activated renin- angiotensin system (such as volume- and/or salt-depleted patients receiving high doses of diuretics) who are receiving angiotensin receptor blockers, symptomatic hypotension may occur. Correction of this condition prior to administration of Dafiro or close medical supervision at the start of treatment is recommended.

If hypotension occurs with Dafiro, 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 stabilised.

Hyperkalaemia:
Concomitant use with potassium supplements, potassium sparing diuretics, salt substitutes containing potassium, or other medicines that may increase potassium levels (heparin, etc.)
should be used with caution and with frequent monitoring of potassium (see Contra-indications).

Renal artery stenosis:
(See Contra-indications)

Hepatic impairment:
Valsartan is mostly eliminated unchanged via the bile whereas amlodipine is extensively metabolised by the liver. Amlodipine half-life is prolonged in patients with impaired liver function. Particular caution should be exercised when administering Dafiro to patients with hepatic impairment or biliary obstructive disorders. Dafiro containing lower (5 mg) initial dose of amlodipine should be administered in these patients.

Renal impairment:
No dosage adjustment of Dafiro is required for patients with mild to moderate renal impairment. However, no data is available for severe cases (creatinine clearance <10 ml/min.) and caution is therefore advised.

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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT
There is no experience of overdose with Dafiro yet. The major symptom of overdose with valsartan is possibly pronounced hypotension with dizziness. Overdose with amlodipine may result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and potentially prolonged systemic

hypotension up to and including shock with fatal outcome have been reported.

If the ingestion is recent, induction of vomiting or gastric lavage may be considered. Administration of activated charcoal to healthy volunteers immediately or up to two hours after ingestion of amlodipine has been shown to significantly decrease amlodipine absorption. Clinically significant hypotension due to Dafiro overdose calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

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

IDENTIFICATION

Dafiro 5/160 mg: Dark yellow, ovaloid, film-coated tablets with bevelled edges. Debossed with "NVR" on one side and “ECE” on the other.

Dafiro 10/160 mg: Light yellow, ovaloid, film-coated tablets with bevelled edges.Debossed with "NVR” on one side and “UIC” on the other.

Dafiro 5/320 mg: Very dark yellow, ovaloid, film-coated tablets with bevelled edges. Debossed with "NVR” on one side and “CSF” on the other.

Dafiro 10/320 mg: Dark yellow, ovaloid, film-coated tablets with bevelled edges. Debossed with "NVR” on one side and “LUF” on the other.

PRESENTATION

7, 14, 28, 56, 90 or 98 film-coated tablets in PA/Al/PVC (polyamide/aluminium/polyvinylchloride) blisters with an aluminium foil backing. Not all pack sizes may be marketed.

The blister foil is imprinted with the proprietary name, company name, batch number and expiry date.

STORAGE INSTRUCTIONS

Store at or below 30 °C in the original package. Protect from moisture.

Keep out of the reach of children.

REGISTRATION NUMBERS

DAFIRO 5/160 mg tablet: 45/7.1.3/0706

DAFIRO 10/160 mg tablet: 45/7.1.3/0707

DAFIRO 5/320 mg tablet: 45/7.1.3/1011

DAFIRO 10/320 mg tablet: 45/7.1.3/1012

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1]

Waterfall 5-Ir
Magwa Crescent West
Waterfall City
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2090

DATE OF PUBLICATION OF THIS PACKAGE INSERT

26 October 2012

[1]Company Reg. No.: 1990/001979/07