ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Dafiro HCT 5 mg/160 mg/12.5 mg film-coated tablets
Dafiro HCT 10 mg/160 mg/12.5 mg film-coated tablets
Dafiro HCT 5 mg/160 mg/25 mg film-coated tablets
Dafiro HCT 10 mg/160 mg/25 mg film-coated tablets
Dafiro HCT 10 mg/320 mg/25 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Dafiro HCT 5 mg/160 mg/12.5 mg film-coated tablets

Each film-coated tablet contains 5 mg of amlodipine (as amlodipine besylate), 160 mg of valsartan, and 12.5 mg of hydrochlorothiazide.

Dafiro HCT 10 mg/160 mg/12.5 mg film-coated tablets

Each film-coated tablet contains 10 mg of amlodipine (as amlodipine besylate), 160 mg of valsartan, and 12.5 mg of hydrochlorothiazide.

Dafiro HCT 5 mg/160 mg/25 mg film-coated tablets

Each film-coated tablet contains 5 mg of amlodipine (as amlodipine besylate), 160 mg of valsartan, and 25 mg of hydrochlorothiazide.

Dafiro HCT 10 mg/160 mg/25 mg film-coated tablets

Each film-coated tablet contains 10 mg of amlodipine (as amlodipine besylate), 160 mg of valsartan, and 25 mg of hydrochlorothiazide.

Dafiro HCT 10 mg/320 mg/25 mg film-coated tablets

Each film-coated tablet contains 10 mg of amlodipine (as amlodipine besylate), 320 mg of valsartan and 25 mg of hydrochlorothiazide.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Dafiro HCT 5 mg/160 mg/12.5 mg film-coated tablets

White, ovaloid, biconvex tablets with bevelled edge, debossed “NVR” on one side and “VCL” on the other side. Approximate size: 15 mm (length) x 5.9 mm (width).

Dafiro HCT 10 mg/160 mg/12.5 mg film-coated tablets

Pale yellow, ovaloid, biconvex tablets with bevelled edge, debossed “NVR” on one side and “VDL” on the other side. Approximate size: 15 mm (length) x 5.9 mm (width).

Dafiro HCT 5 mg/160 mg/25 mg film-coated tablets

Yellow, ovaloid, biconvex tablets with bevelled edge, debossed “NVR” on one side and “VEL” on the other side. Approximate size: 15 mm (length) x 5.9 mm (width).

Dafiro HCT 10 mg/160 mg/25 mg film-coated tablets

Brown-yellow, ovaloid, biconvex tablets with bevelled edge, debossed “NVR” on one side and “VHL” on the other side. Approximate size: 15 mm (length) x 5.9 mm (width).

Dafiro HCT 10 mg/320 mg/25 mg film-coated tablets

Brown-yellow, ovaloid, biconvex tablets with bevelled edge, debossed “NVR” on one side and “VFL” on the other side. Approximate size: 19 mm (length) x 7.5 mm (width).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension as substitution therapy in adult patients whose blood pressure is adequately controlled on the combination of amlodipine, valsartan and hydrochlorothiazide (HCT), taken either as three single-component formulations or as a dual-component and a single-component formulation.

4.2 Posology and method of administration

Posology

The recommended dose of Dafiro HCT is one tablet per day, to be taken preferably in the morning.

Before switching to Dafiro HCT patients should be controlled on stable doses of the monocomponents taken at the same time. The dose of Dafiro HCT should be based on the doses of the individual components of the combination at the time of switching.

The maximum recommended dose of Dafiro HCT is 10 mg/320 mg/25 mg.

Special populations
Renal impairment
Due to the hydrochlorothiazide component, Dafiro HCT is contraindicated for use in patients with anuria (see section 4.3) and in patients with severe renal impairment (glomerular filtration rate (GFR) <30 ml/min/1.73 m^2) (see sections 4.3, 4.4 and 5.2).

No adjustment of the initial dose is required for patients with mild to moderate renal impairment (see sections 4.4 and 5.2).

Hepatic impairment
Due to the valsartan component, Dafiro HCT is contraindicated in patients with severe hepatic impairment (see section 4.3). In patients with mild to moderate hepatic impairment without cholestasis, the maximum recommended dose is 80 mg valsartan and therefore Dafiro HCT is not suitable in this group of patients (see sections 4.3, 4.4 and 5.2). Amlodipine dose recommendations have not been established in patients with mild to moderate hepatic impairment. When switching eligible hypertensive patients (see section 4.1) with hepatic impairment to Dafiro HCT, the lowest available dose of the amlodipine component should be used.

Heart failure and coronary artery disease
There is limited experience with the use of Dafiro HCT, particulary at the maximum dose, in patients with heart failure and coronary artery disease. Caution is advised in patients with heart failure and coronary artery disease, particularly at the maximum dose of Dafiro HCT, 10 mg/320 mg/25 mg.

Elderly (age 65 years or over)
Caution, including more frequent monitoring of blood pressure, is recommended in elderly patients, particularly at the maximum dose of Dafiro HCT, 10 mg/320 mg/25 mg, since available data in this patient population are limited. When switching eligible elderly hypertensive patients (see section 4.1) to Dafiro HCT, the lowest available dose of the amlodipine component should be used.

Paediatric population
There is no relevant use of Dafiro HCT in the paediatric population (patients below age 18 years) for the indication of essential hypertension.

Method of administration

Oral use.
Dafiro HCT can be taken with or without food.
The tablets should be swallowed whole with some water, at the same time of the day and preferably in the morning.

4.3 Contraindications

- Hypersensitivity to the active substances, to other sulphonamide derivatives, to dihydropyridine derivatives, or to any of the excipients listed in section 6.1.
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6).
- Hepatic impairment, biliary cirrhosis or cholestasis.
- Severe renal impairment (GFR <30 ml/min/1.73 m^2), anuria and patients undergoing dialysis.
- Concomitant use of Dafiro HCT with aliskiren-containing products in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) (see sections 4.5 and 5.1).
- Refractory hypokalaemia, hyponatraemia, hypercalcaemia, and symptomatic hyperuricaemia.
- Severe hypotension.
- Shock (including cardiogenic shock).
- Obstruction of the outflow tract of the left ventricle (e.g. hypertrophic obstructive cardiomyopathy and high grade aortic stenosis).
- Haemodynamically unstable heart failure after acute myocardial infarction.

4.4 Special warnings and precautions for use

The safety and efficacy of amlodipine in hypertensive crisis have not been established.

Sodium- and/or volume-depleted patients

Excessive hypotension, including orthostatic hypotension, was seen in 1.7% of patients treated with the maximum dose of Dafiro HCT (10 mg/320 mg/25 mg) compared to 1.8% of valsartan/hydrochlorothiazide (320 mg/25 mg) patients, 0.4% of amlodipine/valsartan (10 mg/320 mg) patients, and 0.2% of hydrochlorothiazide/amlodipine (25 mg/10 mg) patients in a controlled trial in patients with moderate to severe uncomplicated hypertension.

In sodium-depleted and/or volume-depleted patients, such as those receiving high doses of diuretics, symptomatic hypotension may occur after initiation of treatment with Dafiro HCT. Dafiro HCT should be used only after correction of any pre-existing sodium and/or volume depletion.

If excessive hypotension occurs with Dafiro HCT, 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 been stabilised.

Serum electrolyte changes

Amlodipine/valsartan/hydrochlorothiazide
In the controlled trial of Dafiro HCT, the counteracting effects of valsartan 320 mg and hydrochlorothiazide 25 mg on serum potassium approximately balanced each other in many patients. In other patients, one or the other effect may be dominant. Periodic determinations of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

Periodic determination of serum electrolytes and potassium in particular should be performed at appropriate intervals to detect possible electrolyte imbalance, especially in patients with other risk factors such as impaired renal function, treatment with other medicinal products or history of prior electrolyte imbalances.

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

Hydrochlorothiazide
Treatment with Dafiro HCT should only start after correction of hypokalaemia and any coexisting hypomagnesaemia. Thiazide diuretics can precipitate new onset hypokalaemia or exacerbate pre-existing hypokalaemia. Thiazide diuretics should be administered with caution in patients with conditions involving enhanced potassium loss, for example salt-losing nephropathies and prerenal (cardiogenic) impairment of kidney function. If hypokalaemia develops during hydrochlorothiazide therapy, Dafiro HCT should be discontinued until stable correction of the potassium balance.

Thiazide diuretics can precipitate new onset hyponatraemia and hypochloroaemic alkalosis or exacerbate pre-existing hyponatraemia. Hyponatraemia, accompanied by neurological symptoms (nausea, progressive disorientation, apathy) has been observed. Treatment with hydrochlorothiazide should only be started after correction of pre-existing hyponatraemia. In case severe or rapid hyponatraemia develops during Dafiro HCT therapy, the treatment should be discontinued until normalisation of natraemia.

All patients receiving thiazide diuretics should be periodically monitored for imbalances in electrolytes, particularly potassium, sodium and magnesium.

Renal impairment

Thiazide diuretics may precipitate azotaemia in patients with chronic kidney disease. When Dafiro HCT is used in patients with renal impairment periodic monitoring of serum electrolytes (including potassium), creatinine and uric acid serum levels is recommended. Dafiro HCT is contraindicated in patients with severe renal impairment, anuria or undergoing dialysis (see section 4.3).

No dose adjustment of Dafiro HCT is required for patients with mild to moderate renal impairment (GFR ≥30 ml/min/1.73 m^2).

Renal artery stenosis

Dafiro HCT should be used with caution to treat hypertension in patients with unilateral or bilateral renal artery stenosis or stenosis to a solitary kidney since blood urea and serum creatinine may increase in such patients.

Kidney transplantation

To date there is no experience of the safe use of Dafiro HCT in patients who have had a recent kidney transplantation.

Hepatic impairment

Valsartan is mostly eliminated unchanged via the bile. The half-life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dose recommendations have not been established. In patients with mild to moderate hepatic impairment without cholestasis, the maximum recommended dose is 80 mg valsartan, and therefore, Dafiro HCT is not suitable in this group of patients (see sections 4.2, 4.3 and 5.2).

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 medicinal products including ACE inhibitors. Dafiro HCT should be discontinued immediately in patients who develop angioedema and should not be re-administered.

Intestinal angioedema

Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists, including valsartan (see section 4.8). These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of angiotensin II receptor antagonists. If intestinal angioedema is diagnosed, valsartan should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred.

Heart failure and coronary artery disease/post-myocardial infarction

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

In a long-term, placebo-controlled study (PRAISE-2) of amlodipine in patients with NYHA (New York Heart Association Classification) 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.

Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

Caution is advised in patients with heart failure and coronary artery disease, particularly at the maximum dose of Dafiro HCT, 10 mg/320 mg/25 mg, since available data in these patient populations is limited.

Aortic and mitral valve stenosis

As with all other vasodilators, special caution is indicated in patients with mitral stenosis or significant aortic stenosis that is not high grade.

Pregnancy

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

Primary hyperaldosteronism

Patients with primary hyperaldosteronism should not be treated with the angiotensin II antagonist valsartan as their renin-angiotensin system is not activated. Therefore, Dafiro HCT is not recommended in this population.

Systemic lupus erythematosus

Thiazide diuretics, including hydrochlorothiazide, have been reported to exacerbate or activate systemic lupus erythematosus.

Other metabolic disturbances

Thiazide diuretics, including hydrochlorothiazide, may alter glucose tolerance and raise serum levels of cholesterol, triglycerides and uric acid. In diabetic patients dosage adjustments of insulin or oral hypoglycaemic agents may be required.

Due to the hydrochlorothiazide component, Dafiro HCT is contraindicated in symptomatic hyperuricaemia. Hydrochlorothiazide may raise the serum uric acid level due to reduced clearance of uric acid and may cause or exacerbate hyperuricaemia as well as precipitate gout in susceptible patients.

Thiazides reduce urinary calcium excretion and may cause intermittant and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Dafiro HCT is contraindicated in patients with hypercalcaemia and should only be used after correction of any pre-existing hypercalcaemia. Dafiro HCT should be discontinued if hypercalcaemia develops during treatment. Serum levels of calcium should be periodically monitored during treatment with thiazides. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Photosensitivity

Cases of photosensitivity reactions have been reported with thiazide diuretics (see section 4.8). If photosensitivity reaction occurs during treatment with Dafiro HCT, it is recommended to stop the treatment. If a readministration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Choroidal effusion, acute myopia and secondary acute angle-closure glaucoma

Hydrochlorothiazide, a sulphonamide, has been associated with an idiosyncratic reaction resulting in choroidal effusion with visual field defect, acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to a week of treatment initiation. Untreated acute-angle closure glaucoma can lead to permanent vision loss.

The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatment may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle closure glaucoma may include a history of sulphonamide or penicillin allergy.

General

Caution should be exercised in patients who have shown prior hypersensitivity to other angiotensin II receptor antagonists. Hypersensitivity reactions to hydrochlorothiazide are more likely in patients with allergy and asthma.

Elderly (age 65 years or over)

Caution, including more frequent monitoring of blood pressure, is recommended in elderly patients, particularly at the maximum dose of Dafiro HCT, 10 mg/320 mg/25 mg, since available data in this patient population are limited.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

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

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

Non-melanoma skin cancer
An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitising actions of hydrochlorothiazide could act as a possible mechanism for NMSC.

Patients taking hydrochlorothiazide should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimise the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of hydrochlorothiazide may also need to be reconsidered in patients who have experienced previous NMSC (see also section 4.8).

Acute respiratory toxicity

Very rare severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS), have been reported after taking hydrochlorothiazide. Pulmonary oedema typically develops within minutes to hours after hydrochlorothiazide intake. At the onset, symptoms include dyspnoea, fever, pulmonary deterioration and hypotension. If diagnosis of ARDS is suspected, Dafiro HCT should be withdrawn, and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

4.5 Interaction with other medicinal products and other forms of interaction

No formal interaction studies with other medicinal products have been performed with Dafiro HCT. Thus, only information on interactions with other medicinal products that are known for the individual active substances is provided in this section.

However, it is important to take into account that Dafiro HCT may increase the hypotensive effect of other antihypertensive agents.

Concomitant use not recommended

Dafiro HCT individual component	**Known interactions with the following agents**	**Effect of the interaction with other medicinal products**
Valsartan and HCT	Lithium	Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors, angiotensin II receptor antagonists including valsartan or thiazides. Since renal clearance of lithium is reduced by thiazides, the risk of lithium toxicity may presumably be increased further with Dafiro HCT. Therefore careful monitoring of serum lithium concentrations is recommended during concomitant use.
Valsartan	Potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels	If a medicinal product that affects potassium levels is considered necessary in combination with valsartan, frequent monitoring of potassium plasma levels is advised.
Amlodipine	Grapefruit or grapefruit juice	Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients, resulting in increased blood pressure lowering effects.

Caution required with concomitant use

Dafiro HCT individual component	**Known interactions with the following agents**	**Effect of the interaction with other medicinal products**
Amlodipine	*CYP3A4 inhibitors* (i.e. ketoconazole, itraconazole, ritonavir)	Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure. The clinical translation of these pharmacokinetic variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.
	CYP3A4 inducers (anticonvulsant agents [e.g. carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone], rifampicin, *Hypericum perforatum* [St. John's wort])	Upon co-administration of known inducers of the CYP3A4, the plasma concentration of amlodipine may vary. Therefore, blood pressure should be monitored and dose regulation considered both during and after concomitant medication particularly with strong CYP3A4 inducers (e.g. rifampicin, hypericum perforatum).
	Simvastatin	Co-administration of multiple doses of 10 mg amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. It is recommended to limit the dose of simvastatin to 20 mg daily in patients on amlodipine.
	Dantrolene (infusion)	In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalaemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalaemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.
	Tacrolimus	There is a risk of increased tacrolimus blood levels when co-administered with amlodipine. In order to avoid toxicity of tacrolimus, administration of amlodipine in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus when appropriate.
Valsartan and HCT	*Non-steroidal anti-inflammatory drugs (NSAIDs), including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors), acetylsalicylic acid (>3 g/day), and non-selective NSAIDs*	NSAIDS can attenuate the antihypertensive effect of both angiotensin II antagonists and hydrochlorothiazide when administered simultaneously. Furthermore, concomitant use of Dafiro HCT and NSAIDs may lead to worsening of renal function and an increase in serum potassium. Therefore, monitoring of renal function at the beginning of the treatment is recommended, as well as adequate hydration of the patient.

Valsartan	*Inhibitors of the uptake transporter (rifampicin, ciclosporin) or efflux transporter (ritonavir)*	The results of an *in vitro* study with human liver tissue indicate that valsartan is a substrate of the hepatic uptake transporter OATP1B1 and of the hepatic efflux transporter MRP2. Co-administration of inhibitors of the uptake transporter (rifampicin, ciclosporin) or efflux transporter (ritonavir) may increase the systemic exposure to valsartan.
HCT	*Alcohol, barbiturates or narcotics*	Concomitant administration of thiazide diuretics with substances that also have a blood pressure lowering effect (e.g. by reducing sympathetic central nervous system activity or direct vasodilatation) may potentiate orthostatic hypotension.
	Amantadine	Thiazides, including hydrochlorothiazide, may increase the risk of adverse reactions caused by amantadine.
	Anticholinergic agents and other medicinal products affecting gastric motility	The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents (e.g. atropine, biperiden), apparently due to a decrease in gastrointestinal motility and the stomach emptying rate. Conversely, it is anticipated that prokinetic substances such as cisapride may decrease the bioavailability of thiazide-type diuretics.
	Antidiabetic agents (e.g. insulin and oral antidiabetic agents) – *Metformin*	Thiazides may alter glucose tolerance. Dose adjustment of the antidiabetic medicinal product may be necessary. Metformin should be used with caution because of the risk of lactic acidosis induced by possible functional renal failure linked to hydrochlorothiazide.
	Beta blockers and diazoxide	Concomitant use of thiazide diuretics, including hydrochlorothiazide, with beta blockers may increase the risk of hyperglycaemia. Thiazide diuretics, including hydrochlorothiazide, may enhance the hyperglycaemic effect of diazoxide.
	Ciclosporin	Concomitant treatment with ciclosporin may increase the risk of hyperuricaemia and gout-type complications.
	Cytotoxic agents	Thiazides, including hydrochlorothiazide, may reduce the renal excretion of cytotoxic agents (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.
	Digitalis glycosides	Thiazide-induced hypokalaemia or hypomagnesaemia may occur as undesirable effects, favouring the onset of digitalis-induced cardiac arrhythmias.
	Iodine contrasting agents	In case of diuretic-induced dehydration, there is an increased risk of acute renal failure, especially with high doses of iodine products. Patients should be re-hydrated before the administration.
	Ion exchange resins	Absorption of thiazide diuretics, including hydrochlorothiazide, is decreased by cholestyramine or colestipol. This could result in sub-therapeutic effects of thiazide diuretics. However, staggering the dosage of hydrochlorothiazide and resin such that hydrochlorothiazide is administered at least 4 hours before or 4-6 hours after the administration of resins would potentially minimise the interaction.

Medicinal products affecting serum potassium level	The hypokalaemic effect of hydrochlorothiazide may be increased by concomitant administration of kaliuretic diuretics, corticosteroids, laxatives, adrenocorticotropic hormone (ACTH), amphotericin, carbenoxolone, penicillin G and salicylic acid derivatives or antiarrhythmics. If these medicinal products are to be prescribed with the amlodipine /valsartan /hydrochlorothiazide combination, monitoring of potassium plasma levels is advised.
Medicinal products affecting serum sodium level	The hyponatraemic effect of diuretics may be intensified by concomitant administration of medicinal products such as antidepressants, antipsychotics, antiepileptics, etc. Caution is indicated in long-term administration of these medicinal products.
Medicinal products that could induce torsades de pointes	Due to the risk of hypokalaemia, hydrochlorothiazide should be administered with caution when associated with medicinal products that could induce *torsades de pointes*, in particular Class Ia and Class III antiarrhythmics and some antipsychotics.
Medicinal products used in the treatment of gout (probenecid, sulfinpyrazone and allopurinol)	Dose adjustment of uricosuric medicinal products may be necessary as hydrochlorothiazide may raise the level of serum uric acid. Increase of dose of probenecid or sulfinpyrazone may be necessary. Co-administration of thiazide diuretics, including hydrochlorothiazide, may increase the incidence of hypersensitivity reactions to allopurinol.
Methyldopa	There have been isolated reports of haemolytic anaemia occurring with concomitant use of hydrochlorothiazide and methyldopa.
Non-depolarising skeletal muscle relaxants (e.g. tubocurarine)	Thiazides, including hydrochlorothiazide, potentiate the action of curare derivatives.
Other anti-hypertensive medicinal products	Thiazides potentiate the antihypertensive action of other antihypertensive drugs (e.g. guanethidine, methyldopa, beta-blockers, vasodilators, calcium channel blockers, ACE inhibitors, ARBs and Direct Renin Inhibitors [DRIs]).
Pressor amines (e.g. noradrenaline, adrenaline)	Hydrochlorothiazide may reduce the response to pressor amines such as noradrenaline. The clinical significance of this effect is uncertain and not sufficient to preclude their use.
Vitamin D and calcium salts	Administration of thiazide diuretics, including hydrochlorothiazide, with vitamin D or with calcium salts may potentiate the rise in serum calcium. Concomitant use of thiazide type diuretics may lead to hypercalcaemia in patients pre-disposed for hypercalcaemia (e.g. hyperparathyroidism, malignancy or vitamin-D-mediated conditions) by increasing tubular calcium reabsorption.

Dual blockade of the RAAS with ARBs, ACE inhibitors or aliskiren

Clinical trial data have shown that dual blockade of the RAAS through the combined use of ACE inhibitors, ARBs or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3, 4.4 and 5.1).

4.6 Fertility, pregnancy and lactation

Pregnancy

Amlodipine
The safety of amlodipine in human pregnancy has not been established. In animal studies, reproductive toxicity was observed at high doses (see section 5.3). Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus.

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

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

Exposure to AIIRAs therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3).

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

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

Hydrochlorothiazide
There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient.

Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide, its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.

Amlodipine/valsartan/hydrochlorothiazide
There is no experience on the use of Dafiro HCT in pregnant women. Based on the existing data with the components, the use of Dafiro HCT is not recommended during first trimester and contra-indicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4).

Breast-feeding

Amlodipine is excreted in human milk. The proportion of the maternal dose received by the infant has been estimated with an interquartile range of 3-7%, with a maximum of 15%. The effect of amlodipine on infants is unknown. No information is available regarding the use of valsartan during breast-feeding. Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit milk production. The use of Dafiro HCT during breast-feeding is not recommended. If Dafiro HCT is used during breast-feeding, doses should be kept as low as possible. Alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

Fertility

There are no clinical studies on fertility with Dafiro HCT.

Valsartan
Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day. This dose is 6 times the maximum recommended human dose on a mg/m^2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient).

Amlodipine
Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Patients taking Dafiro HCT and driving vehicles or using machines should take into account that dizziness or weariness may occasionally occur.

Amlodipine can have mild or moderate influence on the ability to drive and use machines. If patients taking Dafiro HCT suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired.

4.8 Undesirable effects

The safety profile of Dafiro HCT presented below is based on clinical studies performed with Dafiro HCT and the known safety profile of the individual components amlodipine, valsartan and hydrochlorothiazide.

Summary of the safety profile

The safety of Dafiro HCT has been evaluated at its maximum dose of 10 mg/320 mg/25 mg in one controlled short-term (8 weeks) clinical study with 2,271 patients, 582 of whom received valsartan in combination with amlodipine and hydrochlorothiazide. Adverse reactions were generally mild and transient in nature and only infrequently required discontinuation of therapy. In this active controlled clinical trial, the most common reasons for discontinuation of therapy with Dafiro HCT were dizziness and hypotension (0.7%).

In the 8-week controlled clinical study, no significant new or unexpected adverse reactions were observed with triple therapy treatment compared to the known effects of the monotherapy or dual therapy components.

In the 8-week controlled clinical study, changes in laboratory parameters observed with the combination of Dafiro HCT were minor and consistent with the pharmacological mechanism of action of the monotherapy agents. The presence of valsartan in the triple combination attenuated the hypokalaemic effect of hydrochlorothiazide.

Tabulated list of adverse reactions

The following adverse reactions, listed by MedDRA System Organ Class and frequency, concern Dafiro HCT (amlodipine/valsartan/HCT) and amlodipine, valsartan and HCT individually.
Very common: ≥1/10; common: ≥1/100 to <1/10; uncommon: ≥1/1,000 to <1/100; rare: ≥1/10,000 to <1/1,000; very rare: <1/10,000, not known (cannot be estimated from the available data).

MedDRA System Organ Class	**Adverse reactions**	**Frequency**			
		Dafiro HCT	**Amlodipine**	**Valsartan**	**HCT**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma)	--	--	--	Not known
Blood and lymphatic system disorders	Agranulocytosis, bone marrow failure	--	--	--	Very rare
	Haemoglobin and haematocrit decreased	--	--	Not known	--
	Haemolytic anaemia	--	--	--	Very rare
	Leukopenia	--	Very rare	--	Very rare
	Neutropenia	--	--	Not known	--
	Thrombocytopenia, sometimes with purpura	--	Very rare	Not known	Rare
	Aplastic anaemia	--	--	--	Not known
Immune system disorders	Hypersensitivity	--	Very rare	Not known	Very rare
Metabolism and nutrition disorders	Anorexia	Uncommon	--	--	--
	Hypercalcaemia	Uncommon	--	--	Rare
	Hyperglycaemia	--	Very rare	--	Rare
	Hyperlipidaemia	Uncommon	--	--	--
	Hyperuricaemia	Uncommon	--	--	Common
	Hypochloraemic alkalosis	--	--	--	Very rare
	Hypokalaemia	Common	--	--	Very common
	Hypomagnesaemia	--	--	--	Common
	Hyponatraemia	Uncommon	--	--	Common
	Worsening of diabetic metabolic state	--	--	--	Rare
Psychiatric disorders	Depression	--	Uncommon	--	Rare
	Insomnia/sleep disorders	Uncommon	Uncommon	--	Rare
	Mood swings	--	Uncommon	--	
	Confusion	--	Rare	--	--

Nervous system disorders	Coordination abnormal	Uncommon	--	--	--
	Dizziness	Common	Common	--	Rare
	Dizziness postural, dizziness exertional	Uncommon	--	--	--
	Dysgeusia	Uncommon	Uncommon	--	--
	Extrapyramidal syndrome	--	Not known	--	--
	Headache	Common	Common	--	Rare
	Hypertonia	--	Very rare	--	--
	Lethargy	Uncommon	--	--	--
	Paraesthesia	Uncommon	Uncommon	--	Rare
	Peripheral neuropathy, neuropathy	Uncommon	Very rare	--	--
	Somnolence	Uncommon	Common	--	--
	Syncope	Uncommon	Uncommon	--	--
	Tremor	--	Uncommon	--	--
	Hypoesthesia	--	Uncommon	--	--
Eye disorders	Acute angle-closure glaucoma	--	--	--	Not known
	Visual disturbance	--	Uncommon	--	--
	Visual impairment	Uncommon	Uncommon	--	Rare
	Choroidal effusion	--	--	--	Not Known
Ear and labyrinth disorders	Tinnitus	--	Uncommon	--	--
	Vertigo	Uncommon	--	Uncommon	--
Cardiac disorders	Palpitations	--	Common	--	--
	Tachycardia	Uncommon	--	--	--
	Arrhythmias (including bradycardia, ventricular tachycardia, and atrial fibrillation)	--	Very rare	--	Rare
	Myocardial infarction	--	Very rare	--	--
Vascular disorders	Flushing	--	Common	--	--
	Hypotension	Common	Uncommon	--	--
	Orthostatic hypotension	Uncommon	--	--	Common
	Phlebitis, thrombophlebitis	Uncommon	--	--	--
	Vasculitis	--	Very rare	Not known	--
Respiratory, thoracic and mediastinal disorders	Cough	Uncommon	Very rare	Uncommon	--
	Dyspnoea	Uncommon	Uncommon	--	--
	Acute respiratory distress syndrome (ARDS) (see section 4.4)	--	--	--	Very rare
	Respiratory distress, pulmonary oedema, pneumonitis	--	--	--	Very rare
	Rhinitis	--	Uncommon	--	--
	Throat irritation	Uncommon	--	--	--

Gastrointestinal disorders	Abdominal discomfort, abdominal pain upper	Uncommon	Common	Uncommon	Rare
	Breath odour	Uncommon	--	--	--
	Change of bowel habit	--	Uncommon	--	--
	Constipation	--	--	--	Rare
	Decreased appetite	--	--	--	Common
	Diarrhoea	Uncommon	Uncommon	--	Rare
	Dry mouth	Uncommon	Uncommon	--	--
	Dyspepsia	Common	Uncommon	--	--
	Gastritis	--	Very rare	--	--
	Gingival hyperplasia	--	Very rare	--	--
	Nausea	Uncommon	Common	--	Common
	Pancreatitis	--	Very rare	--	Very rare
	Vomiting	Uncommon	Uncommon	--	Common
	Intestinal angioedema	--	--	Very rare	--
Hepatobiliary disorders	Liver function test abnormal, including blood bilirubin increase	--	Very rare**	Not known	--
	Hepatitis	--	Very rare	--	--
	Intrahepatic cholestasis, jaundice	--	Very rare	--	Rare
Skin and subcutaneous tissue disorders	Alopecia	--	Uncommon	--	
	Angioedema	--	Very rare	Not known	--
	Dermatitis bullous	--	--	Not known	--
	Cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus	--	--	--	Very rare
	Erythema multiforme	--	Very rare	--	Not known
	Exanthema	--	Uncommon	--	--
	Hyperhidrosis	Uncommon	Uncommon	--	--
	Photosensitivity reaction*	--	Very rare	--	Rare
	Pruritus	Uncommon	Uncommon	Not known	--
	Purpura	--	Uncommon	--	Rare
	Rash	--	Uncommon	Not known	Common
	Skin discoloration	--	Uncommon	--	--
	Urticaria and other forms of rash	--	Very rare	--	Common
	Vasculitis necrotising and toxic epidermal necrolysis	--	Not known	--	Very rare
	Exfoliative dermatitis	--	Very rare	--	--
	Stevens-Johnson syndrome	--	Very rare	--	--
	Quincke oedema	--	Very rare	--	--
Musculoskeletal and connective tissue disorders	Arthralgia	--	Uncommon	--	--
	Back pain	Uncommon	Uncommon	--	--
	Joint swelling	Uncommon	--	--	--
	Muscle spasm	Uncommon	Uncommon	--	Not known
	Muscular weakness	Uncommon	--	--	--
	Myalgia	Uncommon	Uncommon	Not known	--
	Pain in extremity	Uncommon	--	--	--
	Ankle swelling	--	Common	--	--

Renal and urinary disorders	Blood creatinine increased	Uncommon	--	Not known	--
	Micturition disorder		Uncommon		
	Nocturia	--	Uncommon	--	--
	Pollakiuria	Common	Uncommon		
	Renal dysfunction	--	--	--	Not known
	Acute renal failure	Uncommon	--	--	Not known
	Renal failure and impairment	--	--	Not known	Rare
Reproductive system and breast disorders	Impotence	Uncommon	Uncommon	--	Common
	Gynaecomastia		Uncommon	--	--
General disorders and administration site conditions	Abasia, gait disturbance	Uncommon	--	--	--
	Asthenia	Uncommon	Uncommon	--	Not known
	Discomfort, malaise	Uncommon	Uncommon	--	--
	Fatigue	Common	Common	Uncommon	--
	Non cardiac chest pain	Uncommon	Uncommon	--	--
	Oedema	Common	Common	--	--
	Pain	--	Uncommon	--	--
	Pyrexia	--	--	--	Not known
Investigations	Lipids increased		--		Very common
	Blood urea nitrogen increased	Uncommon	--	--	--
	Blood uric acid increased	Uncommon	--	--	
	Glycosuria				Rare
	Blood potassium decreased	Uncommon	--	--	--
	Blood potassium increased	--	--	Not known	--
	Weight increase	Uncommon	Uncommon	--	--
	Weight decrease	--	Uncommon	--	--

* See section 4.4 Photosensitivity
** Mostly consistent with cholestasis

Description of selected adverse reactions

Non-melanoma skin cancer: based on available data from epidemiological studies, cumulative dose-dependent association between hydrochlorothiazide and NMSC has been observed (see also sections 4.4 and 5.1).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms

There is no experience of overdose with Dafiro HCT. The major symptom of overdose with valsartan is possibly pronounced hypotension with dizziness. Overdose with amlodipine may result in excessive peripheral vasodilation and, possibly, reflex tachycardia. Marked and potentially prolonged systemic hypotension, including shock with fatal outcome, have been reported with amlodipine.

Non-cardiogenic pulmonary oedema has rarely been reported as a consequence of amlodipine overdose that may manifest with a delayed onset (24-48 hours post-ingestion) and require ventilatory support. Early resuscitative measures (including fluid overload) to maintain perfusion and cardiac output may be precipitating factors.

Treatment

Amlodipine/Valsartan/Hydrochlorothiazide
Clinically significant hypotension due to Dafiro HCT 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.

Amlodipine
If 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.
Amlodipine is unlikely to be removed by haemodialysis.

Valsartan
Valsartan is unlikely to be removed by haemodialysis.

Hydrochlorothiazide
Overdose with hydrochlorothiazide is associated with electrolyte depletion (hypokalaemia, hypochloraemia) and hypovolaemia resulting from excessive diuresis. The most common signs and symptoms of overdose are nausea and somnolence. Hypokalaemia may result in muscle spasms and or accentuate arrhythmia associated with the concomitant use of digitalis glycosides or certain anti-arrhythmic medicinal products.
The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, angiotensin II antagonists, other combinations, ATC code: C09DX01.

Mechanism of action

Dafiro HCT combines three antihypertensive compounds with complementary mechanisms to control blood pressure in patients with essential hypertension: amlodipine belongs to the calcium antagonist class and valsartan to the angiotensin II antagonist class of medicines and hydrochlorothiazide belongs to the thiazide diuretics class of medicines. The combination of these substances has an additive antihypertensive effect.

Amlodipine/Valsartan/Hydrochlorothiazide

Clinical efficacy and safety
Dafiro HCT was studied in a double-blind, active controlled study in hypertensive patients. A total of 2,271 patients with moderate to severe hypertension (mean baseline systolic/diastolic blood pressure was 170/107 mmHg) received treatments of amlodipine/valsartan/hydrochlorothiazide 10 mg/320 mg/25 mg, valsartan/hydrochlorothiazide 320 mg/25 mg, amlodipine/valsartan 10 mg/320 mg, or hydrochlorothiazide/amlodipine 25 mg/10 mg. At study initiation patients were assigned lower doses of their treatment combination and were titrated to their full treatment dose by week 2.

At week 8, the mean reductions in systolic/diastolic blood pressure were 39.7/24.7 mmHg with Dafiro HCT, 32.0/19.7 mmHg with valsartan/hydrochlorothiazide, 33.5/21.5 mmHg with amlodipine/valsartan, and 31.5/19.5 mmHg with amlodipine/hydrochlorothiazide. The triple combination therapy was statistically superior to each of the three dual combination treatments in reduction of diastolic and systolic blood pressures. The reductions in systolic/diastolic blood pressure with Dafiro HCT were 7.6/5.0 mmHg greater than with valsartan/hydrochlorothiazide, 6.2/3.3 mmHg greater than with amlodipine/valsartan, and 8.2/5.3 mmHg greater than with amlodipine/hydrochlorothiazide. The full blood pressure lowering effect was achieved 2 weeks after being on their maximal dose of Dafiro HCT. Statistically greater proportions of patients achieved blood pressure control (<140/90 mmHg) with Dafiro HCT (71%) compared to each of the three dual combination therapies (45-54%) ($p<0.0001$).

In a subgroup of 283 patients focusing on ambulatory blood pressure monitoring, clinically and statistically superior reductions in 24-hour systolic and diastolic blood pressures were observed with the triple combination compared to valsartan/hydrochlorothiazide, valsartan/amlodipine, and hydrochlorothiazide/amlodipine.

Amlodipine

Mechanism of action
The amlodipine component of Dafiro HCT 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 reductions in peripheral vascular resistance and in blood pressure.

Pharmacodynamic effects
Experimental data suggest that amlodipine binds to both dihydropyridine and non-dihydropyridine 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 vasodilation, 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 increases in glomerular filtration rate and effective renal plasma flow, without change in filtration fraction or proteinuria.

As with other calcium channel blockers, 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 to intact animals and humans, even when co-administered with beta blockers to humans.

Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or humans. In clinical studies in which amlodipine was administered in combination with beta blockers to patients with either hypertension or angina, no adverse effects on electrocardiographic parameters were observed.

Amlodipine has been studied in patients with chronic stable angina, vasospastic angina and angiographically documented coronary artery disease.

Clinical efficacy and safety
Use in patients with hypertension
A randomised double-blind morbidity-mortality study called the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) was performed to compare newer therapies: amlodipine 2.5-10 mg/day (calcium channel blocker) or lisinopril 10-40 mg/day (ACE-inhibitor) as first-line therapies to that of the thiazide-diuretic, chlorthalidone 12.5-25 mg/day in mild to moderate hypertension.

A total of 33,357 hypertensive patients aged 55 or older were randomised and followed for a mean of 4.9 years. The patients had at least one additional coronary heart disease risk factor, including: previous myocardial infarction or stroke (>6 months prior to enrollment) or documentation of other atherosclerotic cardiovascular disease (overall 51.5%), type 2 diabetes (36.1%), high density lipoprotein - cholesterol <35 mg/dl or <0.906 mmol/l (11.6%), left ventricular hypertrophy diagnosed by electrocardiogram or echocardiography (20.9%), current cigarette smoking (21.9%).

The primary endpoint was a composite of fatal coronary heart disease or non-fatal myocardial infarction. There was no significant difference in the primary endpoint between amlodipine-based therapy and chlorthalidone-based therapy: risk ratio (RR) 0.98 95% CI (0.90-1.07) p=0.65. Among secondary endpoints, the incidence of heart failure (component of a composite combined cardiovascular endpoint) was significantly higher in the amlodipine group as compared to the chlorthalidone group (10.2% versus 7.7%, RR 1.38, 95% CI [1.25-1.52] p<0.001). However, there was no significant difference in all-cause mortality between amlodipine-based therapy and chlorthalidone-based therapy RR 0.96 95% CI [0.89-1.02] p=0.20.

Valsartan

Mechanism of action
Valsartan is an orally active, potent and specific angiotensin II receptor antagonist. It acts selectively on the receptor subtype AT_1, which is responsible for the known actions of angiotensin II.

Clinical efficacy and safety
Administration of valsartan to patients with hypertension results in a drop in 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 drop in 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.

Hydrochlorothiazide

Mechanism of action
The site of action of thiazide diuretics is primarily in the renal distal convoluted tubule. It has been shown that there is a high-affinity receptor in the renal cortex as the primary binding site for the thiazide diuretic action and inhibition of NaCl transport in the distal convoluted tubule. The mode of action of thiazides is through inhibition of the Na^+Cl^- symporter perhaps by competing for the Cl^- site, thereby affecting electrolyte reabsorption mechanisms: directly increasing sodium and chloride excretion to an approximately equal extent, and indirectly, by this diuretic action, reducing plasma volume, with consequent increases in plasma renin activity, aldosterone secretion and urinary potassium loss, and a decrease in serum potassium.

Non-melanoma skin cancer
Based on available data from epidemiological studies, cumulative dose-dependent association between hydrochlorothiazide and NMSC has been observed. One study included a population comprised of 71,533 cases of BCC and of 8,629 cases of SCC matched to 1,430,833 and 172,462 population controls, respectively. High hydrochlorothiazide use (≥50000 mg cumulative) was associated with an adjusted odds ratio (OR) of 1.29 (95% CI: 1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for SCC. A clear cumulative dose response relationship was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to hydrochlorothiazide: 633 cases of lip cancer were matched with 63,067 population controls, using a risk-set sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR 2.1 (95% CI: 1.7-2.6) increasing to OR 3.9 (3.0-4.9) for high use (~25000 mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose (~100000 mg) (see also section 4.4).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Dafiro HCT in all subsets of the paediatric population in essential hypertension (see section 4.2 for information on paediatric use).

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

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

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

These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE inhibitors and ARBs.

ACE inhibitors and ARBs should therefore not be used concomitantly in patients with diabetic nephropathy (see section 4.4).

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

5.2 Pharmacokinetic properties

Linearity

Amlodipine, valsartan and hydrochlorothiazide exhibit linear pharmacokinetics.

Amlodipine/valsartan/hydrochlorothiazide

Following oral administration of Dafiro HCT in normal healthy adults, peak plasma concentrations of amlodipine, valsartan and hydrochlorothiazide are reached in 6-8 hours, 3 hours, and 2 hours, respectively. The rate and extent of absorption of amlodipine, valsartan and hydrochlorothiazide from Dafiro HCT are the same as when administered as individual dosage forms.

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.

Distribution
Volume of distribution is approximately 21 l/kg. *In vitro* studies with amlodipine have shown that approximately 97.5% of circulating drug is bound to plasma proteins.

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

Elimination
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 per cent 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%. Food decreases exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (C_{max}) by about 50%, although from about 8 h post dosing plasma valsartan concentrations are similar for the fed and fasted groups. This reduction in AUC is not, however, accompanied by a clinically significant reduction in the therapeutic effect, and valsartan can therefore be given either with or without food.

Distribution
The steady-state volume of distribution of valsartan after intravenous administration is about 17 litres, indicating that valsartan 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.

Elimination
Valsartan shows multiexponential decay kinetics ($t_{½\alpha}$ <1 h and $t_{½ß}$ about 9 h). Valsartan is primarily eliminated in faeces (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.

Hydrochlorothiazide

Absorption
The absorption of hydrochlorothiazide, after an oral dose, is rapid (T_{max} about 2 hours). The increase in mean AUC is linear and dose proportional in the therapeutic range.

The effect of food on hydrochlorothiazide absorption, if any, has little clinical significance. Absolute bioavailability of hydrochlorothiazide is 70% after oral administration.

Distribution
The apparent volume of distribution is 4-8 l/kg. Circulating hydrochlorothiazide is bound to serum proteins (40-70%), mainly serum albumin. Hydrochlorothiazide also accumulates in erythrocytes at approximately 3 times the level in plasma.

Biotransformation
Hydrochlorothiazide is eliminated predominantly as unchanged compound.

Elimination
Hydrochlorothiazide is eliminated from plasma with a half-life averaging 6 to 15 hours in the terminal elimination phase. There is no change in the kinetics of hydrochlorothiazide on repeated dosing, and accumulation is minimal when dosed once daily. More than 95% of the absorbed dose is being excreted as unchanged compound in the urine. The renal clearance is composed of passive filtration and active secretion into the renal tubule.

Special populations

Paediatric patients (age below 18 years)
No pharmacokinetic data are available in the paediatric population.

Elderly (age 65 years or over)
Time to peak plasma amlodipine concentrations is similar in young and elderly patients. In elderly patients, amlodipine clearance tends to decline, causing increases in the area under the curve (AUC) and elimination half-life. Mean systemic AUC of valsartan is higher by 70% in the elderly than in the young, therefore caution is required when increasing the dosage.

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.

Limited data suggest that the systemic clearance of hydrochlorothiazide is reduced in both healthy and hypertensive elderly subjects compared to young healthy volunteers.

Since the three components are equally well tolerated in younger and elderly patients, normal dose regimens are recommended (see section 4.2).

Renal impairment
The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. 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.

Patients with mild to moderate renal impairment may therefore receive the usual initial dose (see sections 4.2 and 4.4).

In the presence of renal impairment, mean peak plasma levels and AUC values of hydrochlorothiazide are increased and the urinary excretion rate is reduced. In patients with mild to moderate renal impairment, a 3-fold increase in hydrochlorothiazide AUC has been observed. In patients with severe renal impairment an 8-fold increase in AUC has been observed. Dafiro HCT is contraindicated in patients with severe renal impairment, anuria or undergoing dialysis (see section 4.3).

Hepatic impairment
Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic impairment have decreased clearance of amlodipine with resulting increase 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 that found in healthy volunteers (matched by age, sex and weight). Due to the valsartan component, Dafiro HCT is contraindicated in patients with hepatic impairment (see sections 4.2 and 4.3).

5.3 Preclinical safety data

Amlodipine/Valsartan/Hydrochlorothiazide

In a variety of preclinical safety studies conducted in several animal species with amlodipine, valsartan, hydrochlorothiazide, valsartan/hydrochlorothiazide, amlodipine/valsartan and amlodipine/valsartan/hydrochlorothiazide (Dafiro HCT), there was no evidence of systemic or target organ toxicity that would adversely affect the development of Dafiro HCT for clinical use in humans.

Preclinical safety studies of up to 13 weeks in duration were conducted with amlodipine/valsartan/hydrochlorothiazide in rats. The combination resulted in expected reduction of red blood cell mass (erythrocytes, haemoglobin, haematocrit, and reticulocytes), increase in serum urea, increase in serum creatinine, increase in serum potassium, juxtaglomerular (JG) hyperplasia in the kidney and focal erosions in the glandular stomach in rats. All these changes were reversible after a 4-week recovery period and were considered to be exaggerated pharmacological effects.

The amlodipine/valsartan/hydrochlorothiazide combination was not tested for genotoxicity or carcinogenicity as there was no evidence of any interaction between these substances, which have been on the market for a long time. However, amlodipine, valsartan and hydrochlorothiazide have been tested individually for genotoxicity and carcinogenicity with negative results.

Amlodipine

Reproductive toxicology
Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.

Impairment of fertility
There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m^2 basis). In another rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

Carcinogenesis, mutagenesis
Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m^2 basis) was close to the maximum tolerated dose for mice but not for rats.

Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.

* Based on patient weight of 50 kg

Valsartan

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

In rats, maternally toxic doses (600 mg/kg/day) during the last days of gestation and lactation led to lower survival, lower weight gain and delayed development (pinna detachment and ear-canal opening) in the offspring (see section 4.6). These doses in rats (600 mg/kg/day) are approximately 18 times the maximum recommended human dose on a mg/m^2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient).

In non-clinical safety studies, high doses of valsartan (200 to 600 mg/kg body weight) caused in rats a reduction of red blood cell parameters (erythrocytes, haemoglobin, haematocrit) and evidence of changes in renal haemodynamics (slightly raised 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/m^2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient).

In marmosets at comparable doses, the changes were similar though more severe, particularly in the kidney where the changes developed to a nephropathy including raised 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dafiro HCT 5 mg/160 mg/12.5 mg film-coated tablets

Tablet core
Cellulose microcrystalline
Crospovidone (type A)
Silica, colloidal anhydrous
Magnesium stearate

Coating
Hypromellose, substitution type 2910 (3 mPa.s)
Macrogol 4000
Talc
Titanium dioxide (E171)
Iron oxide, yellow (E172)
Iron oxide, red (E172)

Dafiro HCT 10 mg/160 mg/12.5 mg film-coated tablets

Tablet core
Cellulose microcrystalline
Crospovidone (type A)
Silica, colloidal anhydrous
Magnesium stearate

Coating
Hypromellose, substitution type 2910 (3 mPa.s)
Macrogol 4000
Talc
Titanium dioxide (E171)
Iron oxide, yellow (E172)
Iron oxide, red (E172)

Dafiro HCT 5 mg/160 mg/25 mg film-coated tablets

Tablet core
Cellulose microcrystalline
Crospovidone (type A)
Silica, colloidal anhydrous
Magnesium stearate

Coating
Hypromellose, substitution type 2910 (3 mPa.s)
Macrogol 4000
Talc
Titanium dioxide (E171)
Iron oxide, yellow (E172)

Dafiro HCT 10 mg/160 mg/25 mg film-coated tablets

Tablet core
Cellulose microcrystalline
Crospovidone (type A)
Silica, colloidal anhydrous
Magnesium stearate

Coating
Hypromellose, substitution type 2910 (3 mPa.s)
Macrogol 4000
Talc
Iron oxide, yellow (E172)

Dafiro HCT 10 mg/320 mg/25 mg film-coated tablets

Tablet core
Cellulose microcrystalline
Crospovidone (type A)
Silica, colloidal anhydrous
Magnesium stearate

Coating
Hypromellose, substitution type 2910 (3 mPa.s)
Macrogol 4000
Talc
Iron oxide, yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30°C.

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

PVC/PVDC blisters. One blister contains 7, 10 or 14 film-coated tablets.
Pack sizes: 14, 28, 30, 56, 90, 98 or 280 film-coated tablets.
Multipacks of 280 tablets, comprising 20 cartons, each containing 14 tablets.

PVC/PVDC perforated unit dose blisters for hospital use:
Pack sizes: 56, 98 or 280 film-coated tablets
Multipacks of 280 tablets, comprising 4 cartons, each containing 70 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

Dafiro HCT 5 mg/160 mg/12.5 mg film-coated tablets

EU/1/09/574/001-012

Dafiro HCT 10 mg/160 mg/12.5 mg film-coated tablets

EU/1/09/574/013-024

Dafiro HCT 5 mg/160 mg/25 mg film-coated tablets

EU/1/09/574/025-036

Dafiro HCT 10 mg/160 mg/25 mg film-coated tablets

EU/1/09/574/037-048

Dafiro HCT 10 mg/320 mg/25 mg film-coated tablets

EU/1/09/574/049-060

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 November 2009
Date of latest renewal: 04 July 2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Novartis Farma S.p.A.
Via Provinciale Schito 131
80058 Torre Annunziata (NA)
Italy

Novartis Farmacéutica S.A.
Gran Via de les Corts Catalanes, 764
08013 Barcelona
Spain

Novartis Pharma GmbH
Roonstrasse 25
D-90429 Nürnberg
Germany

Novartis Pharma GmbH
Sophie-Germain-Strasse 10
90443 Nuremberg
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Dafiro HCT 5 mg/160 mg/12.5 mg film-coated tablets
amlodipine/valsartan/hydrochlorothiaziade

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 5 mg amlodipine (as amlodipine besylate), 160 mg valsartan and 12.5 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

14 film-coated tablets
28 film-coated tablets
30 film-coated tablets
56 film-coated tablets
90 film-coated tablets
98 film-coated tablets
280 film-coated tablets
56 x 1 film-coated tablet (unit dose)
98 x 1 film-coated tablet (unit dose)
280 x 1 film-coated tablet (unit dose)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/574/001	14 film-coated tablets
EU/1/09/574/002	28 film-coated tablets
EU/1/09/574/003	30 film-coated tablets
EU/1/09/574/004	56 film-coated tablets
EU/1/09/574/005	90 film-coated tablets
EU/1/09/574/006	98 film-coated tablets
EU/1/09/574/007	280 film-coated tablets
EU/1/09/574/008	56 x 1 film-coated tablet (unit dose)
EU/1/09/574/009	98 x 1 film-coated tablet (unit dose)
EU/1/09/574/010	280 x 1 film-coated tablet (unit dose)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Dafiro HCT 5 mg/160 mg/12.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Dafiro HCT 5 mg/160 mg/12.5 mg film-coated tablets
amlodipine/valsartan/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 5 mg amlodipine (as amlodipine besylate), 160 mg valsartan and 12.5 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

14 film-coated tablets. Component of a multipack. Not to be sold separately.
70x1 film-coated tablets. Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/574/012	280 film-coated tablets (multipack, 20 cartons of 14 tablets)
EU/1/09/574/011	280 film-coated tablets (multipack, 4 cartons of 70 tablets) (unit dose)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Dafiro HCT 5 mg/160 mg/12.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Dafiro HCT 5 mg/160 mg/12.5 mg film-coated tablets
amlodipine/valsartan/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 5 mg amlodipine (as amlodipine besylate), 160 mg valsartan and 12.5 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

Multipack: 280 (20 packs of 14) film-coated tablets.
Multipack: 280 (4 packs of 70x1) film-coated tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/574/012	280 film-coated tablets (multipack, 20 cartons of 14 tablets)
EU/1/09/574/011	280 film-coated tablets (multipack, 4 cartons of 70 tablets) (unit dose)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Dafiro HCT 5 mg/160 mg/12.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Dafiro HCT 5 mg/160 mg/12.5 mg film-coated tablets
amlodipine/valsartan/hydrochlorothiazide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Dafiro HCT 10 mg/160 mg/12.5 mg film-coated tablets
amlodipine/valsartan/hydrochlorothiaziade

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg amlodipine (as amlodipine besylate), 160 mg valsartan and 12.5 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

14 film-coated tablets
28 film-coated tablets
30 film-coated tablets
56 film-coated tablets
90 film-coated tablets
98 film-coated tablets
280 film-coated tablets
56 x 1 film-coated tablet (unit dose)
98 x 1 film-coated tablet (unit dose)
280 x 1 film-coated tablet (unit dose)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/574/013	14 film-coated tablets
EU/1/09/574/014	28 film-coated tablets
EU/1/09/574/015	30 film-coated tablets
EU/1/09/574/016	56 film-coated tablets
EU/1/09/574/017	90 film-coated tablets
EU/1/09/574/018	98 film-coated tablets
EU/1/09/574/019	280 film-coated tablets
EU/1/09/574/020	56 x 1 film-coated tablet (unit dose)
EU/1/09/574/021	98 x 1 film-coated tablet (unit dose)
EU/1/09/574/022	280 x 1 film-coated tablet (unit dose)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Dafiro HCT 10 mg/160 mg/12.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Dafiro HCT 10 mg/160 mg/12.5 mg film-coated tablets
amlodipine/valsartan/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg amlodipine (as amlodipine besylate), 160 mg valsartan and 12.5 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

14 film-coated tablets. Component of a multipack. Not to be sold separately.
70x1 film-coated tablets. Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/574/024	280 film-coated tablets (multipack, 20 cartons of 14 tablets)
EU/1/09/574/023	280 film-coated tablets (multipack, 4 cartons of 70 tablets) (unit dose)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Dafiro HCT 10 mg/160 mg/12.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Dafiro HCT 10 mg/160 mg/12.5 mg film-coated tablets
amlodipine/valsartan/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg amlodipine (as amlodipine besylate), 160 mg valsartan and 12.5 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

Multipack: 280 (20 packs of 14) film-coated tablets.
Multipack: 280 (4 packs of 70x1) film-coated tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/574/024	280 film-coated tablets (multipack, 20 cartons of 14 tablets)
EU/1/09/574/023	280 film-coated tablets (multipack, 4 cartons of 70 tablets) (unit dose)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Dafiro HCT 10 mg/160 mg/12.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Dafiro HCT 10 mg/160 mg/12.5 mg film-coated tablets
amlodipine/valsartan/hydrochlorothiazide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Dafiro HCT 5 mg/160 mg/25 mg film-coated tablets
amlodipine/valsartan/hydrochlorothiaziade

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 5 mg amlodipine (as amlodipine besylate), 160 mg valsartan and 25 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

14 film-coated tablets
28 film-coated tablets
30 film-coated tablets
56 film-coated tablets
90 film-coated tablets
98 film-coated tablets
280 film-coated tablets
56 x 1 film-coated tablet (unit dose)
98 x 1 film-coated tablet (unit dose)
280 x 1 film-coated tablet (unit dose)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/574/025	14 film-coated tablets
EU/1/09/574/026	28 film-coated tablets
EU/1/09/574/027	30 film-coated tablets
EU/1/09/574/028	56 film-coated tablets
EU/1/09/574/029	90 film-coated tablets
EU/1/09/574/030	98 film-coated tablets
EU/1/09/574/031	280 film-coated tablets
EU/1/09/574/032	56 x 1 film-coated tablet (unit dose)
EU/1/09/574/033	98 x 1 film-coated tablet (unit dose)
EU/1/09/574/034	280 x 1 film-coated tablet (unit dose)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Dafiro HCT 5 mg/160 mg/25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Dafiro HCT 5 mg/160 mg/25 mg film-coated tablets
amlodipine/valsartan/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 5 mg amlodipine (as amlodipine besylate), 160 mg valsartan and 25 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

14 film-coated tablets. Component of a multipack: Not to be sold separately.
70x1 film-coated tablets. Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/574/036	280 film-coated tablets (multipack, 20 cartons of 14 tablets)
EU/1/09/574/035	280 film-coated tablets (multipack, 4 cartons of 70 tablets) (unit dose)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Dafiro HCT 5 mg/160 mg/25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Dafiro HCT 5 mg/160 mg/25 mg film-coated tablets
amlodipine/valsartan/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 5 mg amlodipine (as amlodipine besylate), 160 mg valsartan and 25 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

Multipack: 280 (20 packs of 14) film-coated tablets.
Multipack: 280 (4 packs of 70x1) film-coated tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/574/036	280 film-coated tablets (multipack, 20 cartons of 14 tablets)
EU/1/09/574/035	280 film-coated tablets (multipack, 4 cartons of 70 tablets) (unit dose)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Dafiro HCT 5 mg/160 mg/25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Dafiro HCT 5 mg/160 mg/25 mg film-coated tablets
amlodipine/valsartan/hydrochlorothiazide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Dafiro HCT 10 mg/160 mg/25 mg film-coated tablets
amlodipine/valsartan/hydrochlorothiaziade

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg amlodipine (as amlodipine besylate), 160 mg valsartan and 25 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

14 film-coated tablets
28 film-coated tablets
30 film-coated tablets
56 film-coated tablets
90 film-coated tablets
98 film-coated tablets
280 film-coated tablets
56 x 1 film-coated tablet (unit dose)
98 x 1 film-coated tablet (unit dose)
280 x 1 film-coated tablet (unit dose)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/574/037	14 film-coated tablets
EU/1/09/574/038	28 film-coated tablets
EU/1/09/574/039	30 film-coated tablets
EU/1/09/574/040	56 film-coated tablets
EU/1/09/574/041	90 film-coated tablets
EU/1/09/574/042	98 film-coated tablets
EU/1/09/574/043	280 film-coated tablets
EU/1/09/574/044	56 x 1 film-coated tablet (unit dose)
EU/1/09/574/045	98 x 1 film-coated tablet (unit dose)
EU/1/09/574/046	280 x 1 film-coated tablet (unit dose)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Dafiro HCT 10 mg/160 mg/25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Dafiro HCT 10 mg/160 mg/25 mg film-coated tablets
amlodipine/valsartan/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg amlodipine (as amlodipine besylate), 160 mg valsartan and 25 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

14 film-coated tablets. Component of a multipack. Not to be sold separately.
70x1 film-coated tablets. Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/574/048	280 film-coated tablets (multipack, 20 cartons of 14 tablets)
EU/1/09/574/047	280 film-coated tablets (multipack, 4 cartons of 70 tablets) (unit dose)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Dafiro HCT 10 mg/160 mg/25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Dafiro HCT 10 mg/160 mg/25 mg film-coated tablets
amlodipine/valsartan/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg amlodipine (as amlodipine besylate), 160 mg valsartan and 25 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

Multipack: 280 (20 packs of 14) film-coated tablets.
Multipack: 280 (4 packs of 70x1) film-coated tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/574/048	280 film-coated tablets (multipack, 20 cartons of 14 tablets)
EU/1/09/574/047	280 film-coated tablets (multipack, 4 cartons of 70 tablets) (unit dose)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Dafiro HCT 10 mg/160 mg/25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Dafiro HCT 10 mg/160 mg/25 mg film-coated tablets
amlodipine/valsartan/hydrochlorothiazide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Dafiro HCT 10 mg/320 mg/25 mg film-coated tablets
amlodipine/valsartan/hydrochlorothiaziade

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg amlodipine (as amlodipine besylate), 320 mg valsartan and 25 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

14 film-coated tablets
28 film-coated tablets
30 film-coated tablets
56 film-coated tablets
90 film-coated tablets
98 film-coated tablets
280 film-coated tablets
56 x 1 film-coated tablet (unit dose)
98 x 1 film-coated tablet (unit dose)
280 x 1 film-coated tablet (unit dose)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/574/049	14 film-coated tablets
EU/1/09/574/050	28 film-coated tablets
EU/1/09/574/051	30 film-coated tablets
EU/1/09/574/052	56 film-coated tablets
EU/1/09/574/053	90 film-coated tablets
EU/1/09/574/054	98 film-coated tablets
EU/1/09/574/055	280 film-coated tablets
EU/1/09/574/056	56 x 1 film-coated tablet (unit dose)
EU/1/09/574/057	98 x 1 film-coated tablet (unit dose)
EU/1/09/574/058	280 x 1 film-coated tablet (unit dose)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Dafiro HCT 10 mg/320 mg/25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Dafiro HCT 10 mg/320 mg/25 mg film-coated tablets
amlodipine/valsartan/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg amlodipine (as amlodipine besylate), 320 mg valsartan and 25 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

14 film-coated tablets. Component of a multipack: Not to be sold separately.
70x1 film-coated tablets. Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/574/060	280 film-coated tablets (multipack, 20 cartons of 14 tablets)
EU/1/09/574/059	280 film-coated tablets (multipack, 4 cartons of 70 tablets) (unit dose)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Dafiro HCT 10 mg/320 mg/25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Dafiro HCT 10 mg/320 mg/25 mg film-coated tablets
amlodipine/valsartan/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg amlodipine (as amlodipine besylate), 320 mg valsartan and 25 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

Multipack: 280 (20 packs of 14) film-coated tablets.
Multipack: 280 (4 packs of 70x1) film-coated tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/574/060 280 film-coated tablets (multipack, 20 cartons of 14 tablets)
EU/1/09/574/059 280 film-coated tablets (multipack, 4 cartons of 70 tablets) (unit dose)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Dafiro HCT 10 mg/320 mg/25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Dafiro HCT 10 mg/320 mg/25 mg film-coated tablets
amlodipine/valsartan/hydrochlorothiazide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Dafiro HCT 5 mg/160 mg/12.5 mg film-coated tablets
Dafiro HCT 10 mg/160 mg/12.5 mg film-coated tablets
Dafiro HCT 5 mg/160 mg/25 mg film-coated tablets
Dafiro HCT 10 mg/160 mg/25 mg film-coated tablets
Dafiro HCT 10 mg/320 mg/25 mg film-coated tablets
amlodipine/valsartan/hydrochlorothiazide

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Dafiro HCT is and what it is used for
2. What you need to know before you take Dafiro HCT
3. How to take Dafiro HCT
4. Possible side effects
5. How to store Dafiro HCT
6. Contents of the pack and other information

1. What Dafiro HCT is and what it is used for

Dafiro HCT tablets contain three substances called amlodipine, valsartan and hydrochlorothiazide. All of these substances help to control high blood pressure.
- Amlodipine belongs to a group of substances called “calcium channel blockers”. Amlodipine stops calcium from moving into the blood vessel wall, which stops the blood vessels from tightening.
- Valsartan belongs to a group of substances called “angiotensin-II receptor antagonists”. Angiotensin II is produced by the body and makes the blood vessels tighten, thus increasing the blood pressure. Valsartan works by blocking the effect of angiotensin II.
- Hydrochlorothiazide belongs to a group of substances called “thiazide diuretics”. Hydrochlorothiazide increases urine output, which also lowers blood pressure.

As a result of all three mechanisms, the blood vessels relax and blood pressure is lowered.

Dafiro HCT is used to treat high blood pressure in adult patients whose blood pressure is already controlled while taking amlodipine, valsartan and hydrochlorothiazide and who may benefit from taking one tablet containing all three substances.

2. What you need to know before you take Dafiro HCT

Do not take Dafiro HCT
- if you are more than 3 months pregnant. (It is also recommended to avoid Dafiro HCT in early pregnancy – see Pregnancy section.)
- if you are allergic to amlodipine or to any other calcium channel blockers, valsartan, hydrochlorothiazide, sulphonamide-derived medicines (medicines used to treat chest or urinary infections), or any of the other ingredients of this medicine (listed in section 6).
  If you think you may be allergic, do not take Dafiro HCT and talk to your doctor.

- if you have liver disease, destruction of the small bile ducts within the liver (biliary cirrhosis) leading to the build up of bile in the liver (cholestasis).
- if you have **severe** kidney problems or if you are having dialysis.
- if you are unable to produce urine (anuria).
- if the level of potassium or sodium in your blood is too low despite treatment to increase the potassium or sodium levels in your blood.
- if the level of calcium in your blood is too high despite treatment to reduce the calcium levels in your blood.
- if you have gout (uric acid crystals in the joints).
- if you have severe low blood pressure (hypotension).
- if you have narrowing of the aortic valve (aortic stenosis) or cardiogenic shock (a condition where your heart is unable to supply enough blood to the body).
- if you suffer from heart failure after a heart attack.
- if you have diabetes or impaired kidney function and you are treated with a blood pressure lowering medicine containing aliskiren.

If any of the above applies to you, do not take Dafiro HCT and talk to your doctor.

Warnings and precautions

Talk to your doctor or pharmacist before taking Dafiro HCT

- if you have a low level of potassium or magnesium in your blood (with or without symptoms such as muscle weakness, muscle spasms, abnormal heart rhythm).
- if you have a low level of sodium in your blood (with or without symptoms such as tiredness, confusion, muscle twitching, convulsions).
- if you have a high level of calcium in your blood (with or without symptoms such as nausea, vomiting, constipation, stomach pain, frequent urination, thirst, muscle weakness and twitching).
- if you have kidney problems, have had a kidney transplant or if you had been told that you have a narrowing of your kidney arteries.
- if you have liver problems.
- if you have or have had heart failure or coronary artery disease, particularly if you are prescribed the maximum dose of Dafiro HCT (10 mg/320 mg/25 mg).
- if you have experienced a heart attack. Follow your doctor's instructions for the starting dose carefully. Your doctor may also check your kidney function.
- if your doctor has told you that you have a narrowing of the valves in your heart (called "aortic or mitral stenosis") or that the thickness of your heart muscle is abnormally increased (called "obstructive hypertrophic cardiomyopathy").
- if you suffer from aldosteronism. This is a disease in which the adrenal glands make too much of the hormone aldosterone If this applies to you, the use of Dafiro HCT is not recommended.
- if you suffer from a disease called systemic lupus erythematosus (also called "lupus" or "SLE").
- if you have diabetes (high level of sugar in your blood).
- if you have high levels of cholesterol or triglycerides in your blood.
- if you experience skin reactions such as rash after sun exposure.
- if you had an allergic reaction to other high blood pressure medicines or diuretics (a type of medicine also known as "water tablets"), especially if you suffer from asthma and allergies
- if you have been sick (vomiting or diarrhoea).
- if you have experienced swelling, particularly of the face and throat, while taking other medicines (including angiotensin converting enzyme inhibitors). If you get these symptoms, stop taking Dafiro HCT and contact your doctor straight away. You should never take Dafiro HCT again.
- if you experience abdominal pain, nausea, vomiting or diarrhoea after taking Dafiro HCT. Your doctor will decide on further treatment. Do not stop taking Dafiro HCT on your own.
- if you experience dizziness and/or fainting during treatment with Dafiro HCT, tell your doctor as soon as possible.

- if you experience a decrease in vision or eye pain. These could be symptoms of fluid accumulation in the vascular layer of the eye (choroidal effusion) or an increase of pressure in your eye and can happen within hours to a week of taking Dafiro HCT. This can lead to permanent vision impairment, if not treated.
- if you are taking any of the following medicines used to treat high blood pressure:
  - an ACE inhibitor (for example enalapril, lisinopril, ramipril), in particular if you have diabetes-related kidney problems.
  - aliskiren.
- if you have had skin cancer or if you develop an unexpected skin lesion during the treatment. Treatment with hydrochlorothiazide, particularly long term use with high doses, may increase the risk of some types of skin and lip cancer (non-melanoma skin cancer). Protect your skin from sun exposure and UV rays while taking Dafiro HCT.
- if you experienced breathing or lung problems (including inflammation or fluid in the lungs) following hydrochlorothiazide intake in the past. If you develop any severe shortness of breath or difficulty breathing after taking Dafiro HCT, seek medical attention immediately.

Your doctor may check your kidney function, blood pressure, and the amount of electrolytes (e.g. potassium) in your blood at regular intervals.

See also information under the heading “Do not take Dafiro HCT”.

If any of these apply to you, talk to your doctor.

Children and adolescents
The use of Dafiro HCT in children and adolescents under 18 years of age is not recommended.

Elderly people (age 65 years and older)
Dafiro HCT can be used by people aged 65 years and over at the same dose as for other adults and in the same way as they have already taken the three substances called amlodipine, valsartan and hydrochlorothiazide. Elderly patients, particularly those taking the maximum dose of Dafiro HCT (10 mg/320 mg/25 mg), should have their blood pressure checked regularly.

Other medicines and Dafiro HCT
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Your doctor may need to change your dose and/or to take other precautions. In some cases you may have to stop using one of the medicines. This is especially important if you are using any of the medicines listed below:

<u>Do not take together with:</u>
- lithium (a medicine used to treat some types of depression);
- medicines or substances that increase the amount of potassium in your blood. These include potassium supplements or salt substitutes containing potassium, potassium-sparing medicines and heparin;
- ACE inhibitors or aliskiren –(see also information under the headings “Do not take Dafiro HCT” and “Warnings and precautions”) .

<u>Caution should be used with:</u>
- alcohol, sleeping pills and anaesthetics (medicines allowing patients to undergo surgery and other procedures);
- amantadine (anti-Parkinson therapy, also used to treat or prevent certain illnesses caused by viruses);
- anticholinergic agents (medicines used to treat a variety of disorders such as gastrointestinal cramps, urinary bladder spasm, asthma, motion sickness, muscular spasms, Parkinson's disease and as an aid to anaesthesia);
- anticonvulsant medicines and mood-stabilising medicines used to treat epilepsy and bipolar disorder (e.g. carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone);

- cholestyramine, colestipol or other resins (substances used mainly to treat high levels of lipids in the blood);
- simvastatin (a medicine used to control high cholesterol levels);
- ciclosporin (a medicine used in transplantation to prevent organ rejection or for other conditions, e.g: rheumatoid arthritis or atopic dermatitis);
- cytotoxic medicines (used to treat cancer), such as methotrexate or cyclophosphamide;
- digoxin or other digitalis glycosides (medicines used to treat heart problems);
- verapamil, diltiazem (heart medicines);
- iodine contrast media (agents used for imaging examinations);
- medicines for the treatment of diabetes (oral agents such as metformin or insulins);
- medicines for the treatment of gout, such as allopurinol;
- medicines that may increase blood sugar levels (beta blockers, diazoxide);
- medicines that may induce *"torsades de pointes"* (irregular heart beat), such as antiarrhythmics (medicines used to treat heart problems) and some antipsychotics;
- medicines that may reduce the amount of sodium in your blood, such as antidepressants, antipsychotics, antiepileptics;
- medicines that may reduce the amount of potassium in your blood, such as diuretics (water tablets), corticosteroids, laxatives, amphotericin or penicillin G;
- medicines to increase blood pressure such as adrenaline or noradrenaline;
- medicines used for HIV/AIDS (e.g. ritonavir, indinavir, nelfinavir);
- medicines used to treat fungal infections (e.g. ketoconazole, itraconazole);
- medicines used for oesophageal ulceration and inflammation (carbenoxolone);
- medicines used to relieve pain or inflammation, especially non-steroidal anti-inflammatory agents (NSAIDs), including selective cyclooxygenase-2 inhibitors (Cox-2 inhibitors);
- muscle relaxants (medicines to relax the muscles which are used during operations);
- nitroglycerin and other nitrates, or other substances called "vasodilators";
- other medicines to treat high blood pressure, including methyldopa;
- rifampicin (used, for example, to treat tuberculosis), erythromycin, clarithromycin (antibiotics);
- St. John's wort;
- dantrolene (infusion for severe body temperature abnormalities);
- tacrolimus (used to control your body's immune response, enabling your body to accept the transplanted organ);
- vitamin D and calcium salts.

Dafiro HCT with food, drink and alcohol
Grapefruit and grapefruit juice should not be consumed by people who are prescribed Dafiro HCT. This is because grapefruit and grapefruit juice can lead to an increase in the blood levels of the active substance amlodipine, which can cause an unpredictable increase in the blood pressure lowering effect of Dafiro HCT. Talk to your doctor before drinking alcohol. Alcohol may make your blood pressure fall too much and/or increase the possibility of dizziness or fainting.

Pregnancy and breast-feeding
Pregnancy
You must **tell your doctor** if you think you are (or might become) pregnant. Your doctor will normally advise you to stop taking Dafiro HCT before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of Dafiro HCT. Dafiro HCT is not recommended in early pregnancy and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy.

Breast-feeding
Tell your doctor if you are breast-feeding or about to start breast-feeding. Amlodipine has been shown to pass into breast milk in small amounts. Dafiro HCT is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is a newborn, or was born prematurely.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
This medicine may make you feel dizzy, drowsy, nauseous or have a headache. If you experience these symptoms, do not drive or use tools or machines.

3. How to take Dafiro HCT

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure. This will help you get the best results and lower the risk of side effects.

The usual dose of Dafiro HCT is **one tablet** per day.
- It is best to take the tablet at the same time each day. Morning is the best time.
- Swallow the tablet whole with a glass of water.
- You can take Dafiro HCT with or without food. Do not take Dafiro HCT with grapefruit or grapefruit juice.

Depending on how you respond to the treatment, your doctor may suggest a higher or lower dose.

Do not exceed the prescribed dose.

If you take more Dafiro HCT than you should
If you have accidentally taken too many Dafiro HCT tablets, talk to a doctor immediately.You may require medical attention. Excess fluid may accumulate in your lungs (pulmonary oedema) causing shortness of breath that may develop up to 24-48 hours after intake.

If you forget to take Dafiro HCT
If you forget to take a dose of this medicine, take it as soon as you remember and then take the next dose at its usual time. If it is almost time for your next dose you should simply take the next tablet at the usual time. **Do not** take a double dose (two tablets at once) to make up for a forgotten tablet.

If you stop taking Dafiro HCT
Stopping your treatment with Dafiro HCT may cause your disease to get worse. Do not stop taking your medicine unless your doctor tells you to.

Always take this medicine, even if you are feeling well
People who have high blood pressure often do not notice any signs of the problem. Many feel normal. It is very important that you take this medicine exactly as your doctor tells you to get the best results and reduce the risk of side effects. Keep your appointments with the doctor even if you are feeling well.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

As for any combination containing three active substances, side effects associated with each individual component cannot be excluded. The side effects reported with Dafiro HCT or one of its three active substances (amlodipine, valsartan and hydrochlorothiazide) are listed below and may occur with the use of Dafiro HCT.

Some side effects can be serious and need immediate medical attention.
Consult a doctor immediately if you experience any of the following serious side effects after taking this medicine:
Common (may affect up to 1 in 10 people):
- dizziness
- low blood pressure (feeling of faintness, light-headedness, sudden loss of consciousness)

Uncommon (may affect up to 1 in 100 people):
- severely decreased urine output (decreased kidney function)

Rare (may affect up to 1 in 1,000 people):
- spontaneous bleeding
- irregular heart beat
- liver disorder

Very rare (may affect up to 1 in 10,000 people):
- sudden wheeziness, chest pain, shortness of breath or difficulty breathing
- swelling of eyelids, face or lips
- swelling of the tongue and throat which causes great difficulty breathing
- intestinal angioedema: a swelling in the gut presenting with symptoms like abdominal pain, nausea, vomiting and diarrhoea
- severe skin reactions including intense skin rash, hives, reddening of the skin over your whole body, severe itching, blistering, peeling and swelling of the skin, inflammation of the mucous membranes (Stevens-Johnson syndrome, toxic epidermal necrolysis) or other allergic reactions
- acute respiratory distress (signs include severe shortness of breath, fever, weakness, and confusion)
- heart attack
- inflamed pancreas, which may cause severe abdominal and back pain accompanied with feeling of being very unwell
- weakness, bruising, fever and frequent infections
- stiffness

Other side effects may include:
Very common (may affect more than 1 in 10 people):
- low level of potassium in the blood
- increase of lipids in the blood

Common (may affect up to 1 in 10 people):
- sleepiness
- palpitations (awareness of your heart beat)
- flushing
- ankle swelling (oedema)
- abdominal pain
- stomach discomfort after meal
- tiredness

- headache
- frequent urination
- high level of uric acid in the blood
- low level of magnesium in the blood
- low level of sodium in the blood
- dizziness, fainting on standing up
- reduced appetite
- nausea and vomiting
- itchy rash and other types of rash
- inability to achieve or maintain erection

Uncommon (may affect up to 1 in 100 people):
- fast heart beat
- spinning sensation
- vision disorder
- stomach discomfort
- chest pain
- increase of urea nitrogen, creatinine and uric acid in the blood
- high level of calcium, fat or sodium in the blood
- decrease of potassium in the blood
- breath odour
- diarrhoea
- dry mouth
- weight increase
- loss of appetite
- disturbed sense of taste
- back pain
- joint swelling
- muscle cramps/weakness/pain
- pain in extremity
- inability to either stand or walk in a normal manner
- weakness
- abnormal coordination
- dizziness on standing up or after exercising
- lack of energy
- sleep disturbances
- tingling or numbness
- neuropathy
- sudden, temporary loss of consciousness
- low blood pressure on standing up
- cough
- breathlessness
- throat irritation
- excessive sweating
- itching
- swelling, reddening and pain along a vein
- skin reddening
- trembling
- mood changes
- anxiety
- depression
- sleeplessness
- taste abnormalities
- fainting

- loss of pain sensation
- visual disturbances
- visual impairment
- ringing in the ears
- sneezing/runny nose caused by inflammation of the lining of the nose (rhinitis)
- altered bowel habits
- indigestion
- hair loss
- itchy skin
- skin discolouration
- disorder in passing urine
- increased need to urinate at night
- increased number of times of passing urine
- discomfort or enlargement of the breasts in men
- pain
- feeling unwell
- weight decrease

Rare (may affect up to 1 in 1,000 people):
- low level of blood platelets (sometimes with bleeding or bruising underneath the skin)
- sugar in the urine
- high level of sugar in the blood
- worsening of the diabetic metabolic state
- abdominal discomfort
- constipation
- liver disorders which can occur together with yellow skin and eyes, or dark-coloured urine (haemolytic anaemia)
- increased sensitivity of skin to sun
- purple skin patches
- kidney disorders
- confusion

Very rare (may affect up to 1 in 10,000 people):
- decreased number of white blood cells
- decrease in blood platelets which may result in unusual brusing or easy bleeding (red blood cell damage)
- swelling of the gums
- abdominal bloating (gastritis)
- inflammation of the liver (hepatitis)
- yellowing of the skin (jaundice)
- liver enzyme increase which may have an effect on some medical tests
- increased muscle tension
- inflammation of blood vessels often with skin rash
- sensitivity to light
- disorders combining rigidity, tremor and/or movement disorders
- fever, sore throat or mouth ulcers, more frequent infections (lack or low level of white blood cells)
- pale skin, tiredness, breathlessness, dark-coloured urine (haemolytic anaemia, abnormal breakdown of red blood cells either in the blood vessels or elsewhere in the body)

- confusion, tiredness, muscle twitching and spasm, rapid breathing (hypochloraemic alkalosis)
- severe upper stomach ache (inflammation of the pancreas)
- difficulty breathing with fever, coughing, wheezing, breathlessness (respiratory distress, pulmonary oedema, pneumonitis)
- facial rash, joint pain, muscle disorder, fever (lupus erythematosus)
- inflammation of blood vessels with symptoms such as rash, purplish-red spots, fever (vasculitis)
- severe skin disease that causes rash, red skin, blistering of the lips, eyes or mouth, skin peeling, fever (toxic epidermal necrolysis)

Not known (frequency cannot be estimated from the available data):
- changes in blood tests for kidney function, increase of potassium in your blood, low level of red blood cells
- abnormal red blood cell test
- low level of a certain type of white blood cell and blood platelet
- increase of creatinine in the blood
- abnormal liver function test
- severely decreased urine output
- inflammation of blood vessels
- weakness, bruising and frequent infections (aplastic anaemia)
- decrease in vision or pain in your eyes due to high pressure (possible signs of fluid accumulation in the vascular layer of the eye (choroidal effusion) or acute angle-closure glaucoma)
- breathlessness
- severely decreased urine output (possible signs of renal disorder or renal failure)
- severe skin disease that causes rash, red skin, blistering of the lips, eyes or mouth, skin peeling, fever (erythema multiforme)
- muscle spasm
- fever (pyrexia)
- blistering skin (sign of a condition called dermatitis bullous)
- skin and lip cancer (non-melanoma skin cancer)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Dafiro HCT

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.

Do not store above 30°C.

Store in the original package in order to protect from moisture.

Do not use any Dafiro HCT pack that is damaged or shows signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Dafiro HCT contains

Dafiro HCT 5 mg/160 mg/12.5 mg film-coated tablets
The active substances of Dafiro HCT are amlodipine (as amlodipine besylate), valsartan and hydrochlorothiazide. Each film-coated tablet contains 5 mg amlodipine (as amlodipine besylate), 160 mg valsartan and 12.5 mg hydrochlorothiazide.

The other ingredients are cellulose microcrystalline; crospovidone (type A); silica, colloidal anhydrous; magnesium stearate; hypromellose (substitution type 2910 (3 mPa.s)), macrogol 4000, talc, titanium dioxide (E171).

Dafiro HCT 10 mg/160 mg/12.5 mg film-coated tablets
The active substances of Dafiro HCT are amlodipine (as amlodipine besylate), valsartan and hydrochlorothiazide. Each film-coated tablet contains 10 mg amlodipine (as amlodipine besylate), 160 mg valsartan and 12.5 mg hydrochlorothiazide.

The other ingredients are cellulose microcrystalline; crospovidone (type A); silica, colloidal anhydrous; magnesium stearate; hypromellose (substitution type 2910 (3 mPa.s)), macrogol 4000, talc, titanium dioxide (E171), yellow iron oxide (E172), red iron oxide (E172).

Dafiro HCT 5 mg/160 mg/25 mg film-coated tablets
The active substances of Dafiro HCT are amlodipine (as amlodipine besylate), valsartan and hydrochlorothiazide. Each film-coated tablet contains 5 mg amlodipine (as amlodipine besylate), 160 mg valsartan and 25 mg hydrochlorothiazide.

The other ingredients are cellulose microcrystalline; crospovidone (type A); silica, colloidal anhydrous, magnesium stearate, hypromellose (substitution type 2910 (3 mPa.s)), macrogol 4000, talc, titanium dioxide (E171), yellow iron oxide (E172).

Dafiro HCT 10 mg/160 mg/25 mg film-coated tablets
The active substances of Dafiro HCT are amlodipine (as amlodipine besylate), valsartan and hydrochlorothiazide. Each film-coated tablet contains 10 mg amlodipine (as amlodipine besylate), 160 mg valsartan and 25 mg hydrochlorothiazide.

The other ingredients are cellulose microcrystalline; crospovidone (type A); silica, colloidal anhydrous, magnesium stearate, hypromellose (substitution type 2910 (3 mPa.s)), macrogol 4000, talc, yellow iron oxide (E172).

Dafiro 10 mg/320 mg/25 mg film-coated tablets
The active substances of Dafiro HCT are amlodipine (as amlodipine besylate), valsartan and hydrochlorothiazide. Each film-coated tablet contains 10 mg amlodipine (as amlodipine besylate), 320 mg valsartan and 25 mg hydrochlorothiazide.

The other ingredients are cellulose microcrystalline; crospovidone (type A); silica, colloidal anhydrous, magnesium stearate, hypromellose (substitution type 2910 (3 mPa.s)), macrogol 4000, talc, yellow iron oxide (E172).

What Dafiro HCT looks like and contents of the pack
Dafiro HCT 5 mg/160 mg/12.5 mg film-coated tablets are white, oval tablets with “NVR” on one side and “VCL” on the other side. Approximate size: 15 mm (length) x 5.9 mm (width).

Dafiro HCT 10 mg/160 mg/12.5 mg film-coated tablets are pale yellow, oval tablets with “NVR” on one side and “VDL” on the other side. Approximate size: 15 mm (length) x 5.9 mm (width).

Dafiro HCT 5 mg/160 mg/25 mg film-coated tablets are yellow, oval tablets with “NVR” on one side and “VEL” on the other side. Approximate size: 15 mm (length) x 5.9 mm (width).

Dafiro HCT 10 mg/160 mg/25 mg film-coated tablets are brown-yellow, oval tablets with “NVR” on one side and “VHL” on the other side. Approximate size: 15 mm (length) x 5.9 mm (width).

Dafiro HCT 10 mg/320 mg/25 mg film-coated tablets are brown-yellow, oval tablets with “NVR” on one side and “VFL” on the other side. Approximate size: 19 mm (length) x 7.5 mm (width).

Dafiro HCT is available in packs containing 14, 28, 30, 56, 90, 98 or 280 film-coated tablets, in multipacks of 280 tablets (comprising 4 cartons, each containing 70 tablets, or 20 cartons, each containing 14 tablets), and in hospital packs containing 56, 98 or 280 tablets in single perforated dose blisters. Not all pack sizes may be available in your country.

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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu