ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Sprimeo HCT 150 mg/12.5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 150 mg aliskiren (as hemifumarate) and 12.5 mg hydrochlorothiazide.

Excipients: Each tablet contains 25 mg lactose monohydrate and 24.5 mg wheat starch.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

White, biconvex, ovaloid film-coated tablet imprinted with "LCI" on one side and "NVR" on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension in adults.

Sprimeo HCT is indicated in patients whose blood pressure is not adequately controlled on aliskiren or hydrochlorothiazide used alone.

Sprimeo HCT is indicated as substitution therapy in patients adequately controlled with aliskiren and hydrochlorothiazide, given concurrently, at the same dose level as in the combination.

4.2 Posology and method of administration

The recommended dose of Sprimeo HCT is one tablet per day. Sprimeo HCT should be taken with a light meal once a day, preferably at the same time each day. Grapefruit juice should not be taken together with Sprimeo HCT.

The antihypertensive effect is largely manifested within 1 week and the maximum effect is generally seen within 4 weeks.

Posology in patients not adequately controlled with aliskiren or hydrochlorothiazide monotherapy
Individual dose titration with each of the two components may be recommended before changing to the fixed combination. When clinically appropriate, direct change from monotherapy to the fixed combination may be considered.

Sprimeo HCT 150 mg /12.5 mg may be administered in patients whose blood pressure is not adequately controlled with aliskiren 150 mg or hydrochlorothiazide 12.5 mg alone.

If blood pressure remains uncontrolled after 2-4 weeks of therapy, the dose may be titrated up to a maximum of Sprimeo HCT 300 mg/25 mg daily. Dosing should be individualised and adjusted according to the patient's clinical response.

Posology as substitution therapy
For convenience, patients receiving aliskiren and hydrochlorothiazide from separate tablets may be switched to a fixed combination tablet of Sprimeo HCT containing the same component doses.

Renal impairment
No adjustment of the initial dose is required for patients with mild to moderate renal impairment (see sections 4.4 and 5.2). Due to the hydrochlorothiazide component, Sprimeo HCT is contraindicated for use in patients with anuria and in patients with severe renal impairment (glomerular filtration rate (GFR) < 30 ml/min/1.73 m^2). The concomitant use of Sprimeo HCT with angiotensin II receptor blockers (ARB) or angiotensin converting enzyme inhibitors (ACEI) is contraindicated in patients with renal impairment (GFR < 60 ml/min/1.73 m^2) (see sections 4.3, 4.4 and 5.2).

Hepatic impairment
No adjustment of the initial dose is required for patients with mild to moderate hepatic impairment (see section 5.2). Sprimeo HCT is contraindicated in patients with severe hepatic impairment (see sections 4.3 and 4.4).

Elderly patients (over 65 years)
The recommended starting dose of aliskiren in elderly patients is 150 mg. No clinically meaningful additional blood pressure reduction is observed by increasing the dose to 300 mg in the majority of elderly patients.

Paediatric patients
Sprimeo HCT is not recommended for use in children and adolescents below age 18 due to a lack of data on safety and efficacy (see section 5.2).

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients (see section 6.1), or to other sulphonamide-derived substances.
- History of angioedema with aliskiren.
- Hereditary or idiopathic angioedema.
- Second and third trimesters of pregnancy (see section 4.6).
- Anuria.
- Severe renal impairment (GFR < 30 ml/min/1.73 m^2).
- Refractory hypokalaemia, hyponatraemia, hypercalcaemia and symptomatic hyperuricaemia.
- Severe hepatic impairment.
- The concomitant use of aliskiren with ciclosporin and itraconazole, two highly potent P-glycoprotein (P-gp) inhibitors, and other potent P-gp inhibitors (e.g. quinidine), is contraindicated (see section 4.5).
- The concomitant use of aliskiren with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) (see sections 4.2, 4.4, 4.5 and 5.1).

4.4 Special warnings and precautions for use

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
Hypotension, syncope, stroke, hyperkalaemia, and changes in renal function (including acute renal failure) have been reported in susceptible individuals, especially if combining medicinal products that affect this system (see section 5.1). Dual blockade of the renin-angiotensin-aldosterone system by combining aliskiren with an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin II receptor blocker (ARB) is therefore not recommended.

The use of aliskiren in combination with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) (see section 4.3).

Heart failure
Aliskiren should be used with caution in patients with serious congestive heart failure (New York Heart Association (NYHA) functional class III-IV). Sprimeo HCT should be used with caution in patients with heart failure due to limited clinical efficacy and safety data.

Angioedema
As with other agents acting on the renin-angiotensin system, angioedema or symptoms suggestive of angioedema (swelling of the face, lips, throat and/or tongue) have been reported in patients treated with aliskiren.

A number of these patients had a history of angioedema or symptoms suggestive of angioedema, which in some cases followed use of other medicines that can cause angioedema, including RAAS blockers (angiotensin converting enzyme inhibitors or angiotensin receptor blockers) (see section 4.8).

Patients with a history of angioedema may be at increased risk of experiencing angioedema during treatment with aliskiren (see sections 4.3 and 4.8). Caution should therefore be exercised when prescribing aliskiren to patients with a history of angioedema, and such patients should be closely monitored during treatment (see section 4.8) especially at the beginning of the treatment.

If angioedema occurs, Sprimeo HCT should be promptly discontinued and appropriate therapy and monitoring provided until complete and sustained resolution of signs and symptoms has occurred. Where there is involvement of the tongue, glottis or larynx adrenaline should be administered. In addition, measures necessary to maintain patent airways should be provided.

Sodium- and/or volume-depleted patients
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 Sprimeo HCT. Sprimeo HCT should be used only after correction of any pre-existing sodium and/or volume depletion.

Electrolyte imbalance
Treatment with Sprimeo 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 Sprimeo HCT should be discontinued until stable correction of the potassium balance. Although hypokalaemia may develop with the use of thiazide diuretics, concurrent therapy with aliskiren may reduce diuretic-induced hypokalaemia. The risk of hypokalaemia is greater in patients with cirrhosis of the liver, patients experiencing brisk diuresis, patients with inadequate oral electrolyte intake and patients receiving concomitant therapy with corticosteroids or adrenocorticotropic hormone (ACTH) (see sections 4.5 and 4.8).

Conversely, increases in serum potassium have been observed with aliskiren in post-marketing experience and these may be exacerbated by concomitant use of other agents acting on the RAAS or by non-steroidal anti-inflammatory drugs (NSAIDs). Consistent with standard medical practice, periodic determination of renal function including serum electrolytes is advised if co-administration is considered necessary. The concomitant use of aliskiren and ACEIs or ARBs is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) (see sections 4.3, 4.5 and 4.8).

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 Sprimeo HCT therapy, the treatment should be discontinued until normalisation of natraemia.

There is no evidence that Sprimeo HCT would reduce or prevent diuretic-induced hyponatraemia. Chloride deficit is generally mild and usually does not require treatment.

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

Thiazides reduce urinary calcium excretion and may cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Sprimeo HCT is contraindicated in patients with hypercalcaemia and should only be used after correction of any pre-existing hypercalcaemia. Sprimeo 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.

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

No dosage adjustment is necessary in patients with mild to moderate renal impairment (GFR $\geq$ 30 ml/min/1.73 m^2).

There is no experience regarding the administration of Sprimeo HCT in patients who have recently undergone kidney transplantation.

As for other agents acting on the renin-angiotensin system, caution should be exercised when aliskiren is given in the presence of conditions pre-disposing to kidney dysfunction such as hypovolaemia (e.g. due to blood loss, severe or prolonged diarrhoea, prolonged vomiting, etc.), heart disease, liver disease, diabetes mellitus or kidney disease. The concomitant use of aliskiren and ACEIs or ARBs is contraindicated in patients with renal impairment (GFR < 60 ml/min/1.73 m^2). Acute renal failure, reversible upon discontinuation of treatment, has been reported in at-risk patients receiving aliskiren in post-marketing experience. In the event that any signs of renal failure occur, aliskiren should be promptly discontinued.

Hepatic impairment
Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. No adjustment of the initial dose is required for patients with mild to moderate hepatic impairment. No data are available for the use of Sprimeo HCT in patients with severe hepatic impairment. Due to the hydrochlorothiazide component, Sprimeo HCT is contraindicated in patients with severe hepatic impairment (see sections 4.3 and 5.2).

There is no clinical experience with Sprimeo HCT in patients with hepatic impairment.

Moderate P-gp inhibitors
Co-administration of aliskiren 300 mg with ketoconazole 200 mg or verapamil 240 mg resulted in a 76% or 97% increase in aliskiren AUC, respectively. Therefore caution should be exercised when aliskiren is administered with moderate P-gp inhibitors such as ketoconazole or verapamil (see section 4.5).

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy
As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Renal artery stenosis and renovascular hypertension
No controlled clinical data are available on the use of Sprimeo HCT in patients with unilateral or bilateral renal artery stenosis, or stenosis to a solitary kidney. However, as with other agents acting on the renin-angiotensin system, there is an increased risk of renal insufficiency, including acute renal failure, when patients with renal artery stenosis are treated with aliskiren. Therefore caution should be exercised in these patients. If renal failure occurs, treatment should be discontinued.

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

Metabolic and endocrine effects
Thiazide diuretics, including hydrochlorothiazide, may alter glucose tolerance and raise serum levels of cholesterol and triglycerides, and uric acid. In diabetic patients dosage adjustments of insulin or oral hypoglycaemic agents may be required. Concomitant use of Sprimeo HCT with ARBs or ACEIs is contraindicated in patients with diabetes mellitus (see section 4.3).

Due to the hydrochlorothiazide component, Sprimeo HCT is contraindicated in symptomatic hyperuricaemia (see section 4.3). 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 an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Sprimeo HCT is contraindicated in patients with hypercalcaemia and should only be used after correction of any pre-existing hypercalcaemia. Sprimeo 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 Sprimeo HCT, it is recommended to stop the treatment. If a re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Acute angle-closure glaucoma
Hydrochlorothiazide, a sulphonamide, has been associated with an idiosyncratic reaction resulting in 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 weeks 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
In the event of severe and persistent diarrhoea, Sprimeo HCT therapy should be stopped.

As with any antihypertensive agent, excessive reduction of blood pressure in patients with ischaemic cardiopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke.

Hypersensitivity reactions to hydrochlorothiazide may occur in patients, but are more likely in patients with allergy and asthma.

Excipients
Sprimeo HCT contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sprimeo HCT contains wheat starch. It is suitable for people with coeliac disease. Patients with wheat allergy (different from coeliac disease) should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Information on Sprimeo HCT interactions
Medicinal products affecting serum potassium levels: The potassium-depleting effect of hydrochlorothiazide is attenuated by the potassium-sparing effect of aliskiren. However, this effect of hydrochlorothiazide on serum potassium would be expected to be potentiated by other medicinal products associated with potassium loss and hypokalaemia (e.g. other kaliuretic diuretics, corticosteroids, laxatives, adrenocorticotropic hormone (ACTH), amphotericin, carbenoxolone, penicillin G, salicylic acid derivatives). Conversely, concomitant use of other agents affecting the RAAS, of NSAIDs or of agents that increase serum potassium levels (e.g. potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, heparin) may lead to increases in serum potassium. If co-medication with an agent affecting the level of serum potassium is considered necessary, caution is advisable. The combination of aliskiren with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) and is not recommended in other patients (see sections 4.3, 4.4 and 5.1).

Medicinal products affected by serum potassium disturbances: Periodic monitoring of serum potassium is recommended when Sprimeo HCT is administered with medicinal products affected by serum potassium disturbances (e.g. digitalis glycosides, antiarrhythmics).

Non-steroidal anti-inflammatory drugs (NSAIDs), including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors), acetylsalicylic acid and non-selective NSAIDs: As with other agents acting on the renin-angiotensin system, NSAIDs may reduce the anti-hypertensive effect of aliskiren. NSAIDs may also weaken the diuretic and antihypertensive activity of hydrochlorothiazide.

In some patients with compromised renal function (dehydrated patients or elderly patients) aliskiren and hydrochlorothiazide given concomitantly with NSAIDs may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore the use of Sprimeo HCT with an NSAID requires caution, especially in elderly patients.

Other antihypertensive agents: The antihypertensive effect of Sprimeo HCT may be increased with the concomitant use of other antihypertensive agents.

Additional information on aliskiren interactions
The combination of aliskiren with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) and is not recommended in other patients (see sections 4.3, 4.4 and 5.1).

Compounds that have been investigated in aliskiren clinical pharmacokinetic studies include acenocoumarol, atenolol, celecoxib, fenofibrate, pioglitazone, allopurinol, isosorbide-5-mononitrate, digoxin, metformin, amlodipine, atorvastatin, cimetidine and hydrochlorothiazide. No clinically relevant interactions have been identified. As a result no dose adjustment for aliskiren or these co-administered medicinal products is necessary.

P-glycoprotein interactions: MDR1/Mdr1a/1b (P-gp) was found to be the major efflux system involved in intestinal absorption and biliary excretion of aliskiren in preclinical studies. Rifampicin, which is an inducer of P-gp, reduced aliskiren bioavailability by approximately 50% in a clinical study. Other inducers of P-gp (St. John's wort) might decrease the bioavailability of aliskiren. Although this has not been investigated for aliskiren, it is known that P-gp also controls tissue uptake of a variety of substrates and P-gp inhibitors can increase the tissue-to-plasma concentration ratios. Therefore, P-gp inhibitors may increase tissue levels more than plasma levels. The potential for drug interactions at the P-gp site will likely depend on the degree of inhibition of this transporter.

P-gp potent inhibitors: A single dose drug interaction study in healthy subjects has shown that ciclosporin (200 and 600 mg) increases C_{max} of aliskiren 75 mg approximately 2.5-fold and AUC approximately 5-fold. The increase may be higher with higher aliskiren doses. In healthy subjects, itraconazole (100 mg) increases AUC and C_{max} of aliskiren (150 mg) by 6.5-fold and 5.8-fold, respectively. Therefore, concomitant use of aliskiren and P-gp potent inhibitors is contraindicated (see section 4.3).

Moderate P-gp inhibitors: Co-administration of ketoconazole (200 mg) or verapamil (240 mg) with aliskiren (300 mg) resulted in a 76% or 97% increase in aliskiren AUC, respectively. The change in plasma levels of aliskiren in the presence of ketoconazole or verapamil is expected to be within the range that would be achieved if the dose of aliskiren were doubled; aliskiren doses of up to 600 mg, or twice the highest recommended therapeutic dose, have been found to be well tolerated in controlled clinical trials. Preclinical studies indicate that aliskiren and ketoconazole co-administration enhances aliskiren gastrointestinal absorption and decreases biliary excretion. Therefore, caution should be exercised when aliskiren is administered with ketoconazole, verapamil or other moderate P-gp inhibitors (clarithromycin, telithromycin, erythromycin, amiodarone).

P-gp substrates or weak inhibitors: No relevant interactions with atenolol, digoxin, amlodipine or cimetidine have been observed. When administered with atorvastatin (80 mg), steady-state aliskiren (300 mg) AUC and C_{max} increased by 50%.

Organic anion transporting polypeptide (OATP) inhibitors: Preclinical studies indicate that aliskiren might be a substrate of organic anion transporting polypeptides. Therefore, the potential exists for interactions between OATP inhibitors and aliskiren when administered concomitantly (see interaction with Grapefruit juice).

Grapefruit juice: Administration of grapefruit juice with aliskiren resulted in a decrease in AUC and C_{max} of aliskiren. Co-administration with aliskiren 150 mg resulted in a 61% decrease in aliskiren AUC and co-administration with aliskiren 300 mg resulted in a 38% decrease in aliskiren AUC. This decrease is likely due to an inhibition of organic anion transporting polypeptide-mediated uptake of aliskiren by grapefruit juice in the gastrointestinal tract. Therefore, because of the risk of therapeutic failure, grapefruit juice should not be taken together with Sprimeo HCT.

Furosemide: When aliskiren was co-administered with furosemide, the AUC and C_{max} of furosemide were reduced by 28% and 49%, respectively. It is therefore recommended to monitor the effects when initiating and adjusting furosemide therapy to avoid possible underutilisation in clinical situations of volume overload.

Warfarin: The effects of aliskiren on warfarin pharmacokinetics have not been evaluated.

Food interactions: Meals with a high fat content have been shown to reduce the absorption of aliskiren substantially.

Additional information on hydrochlorothiazide interactions
When administered concurrently, the following medicinal products may interact with thiazide diuretics:

Lithium: Renal clearance of lithium is reduced by thiazides, therefore the risk of lithium toxicity may be increased with hydrochlorothiazide. Co-administration of lithium and hydrochlorothiazide is not recommended. If this combination proves essential, careful monitoring of serum lithium level is recommended during concomitant use.

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 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.

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.

Digoxine or other digitalis glycosides: Thiazide-induced hypokalaemia or hypomagnesaemia may occur as undesirable effects, favouring the onset of digitalis-induced cardiac arrhythmias.

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.

Antidiabetic agents (e.g. insulin and oral antidiabetic agents): Thiazides may alter glucose tolerance. Dose adjustment of the antidiabetic medicinal product may be necessary (see section 4.4). 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.

Medicinal products used in the treatment of gout: 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.

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.

Amantadine: Thiazides, including hydrochlorothiazide, may increase the risk of adverse reactions caused by amantadine.

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.

Cytotoxic agents: Thiazides, including hydrochlorothiazide, may reduce the renal excretion of cytotoxic agents (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.

Non-depolarising skeletal muscle relaxants: Thiazides, including hydrochlorothiazide, potentiate the action of skeletal muscle relaxants such as curare derivatives.

Alcohol, barbiturates or narcotics: Concomitant administration of thiazide diuretics with subtances that also have a blood pressure lowering effect (e.g. by reducing sympathetic central nervous system activity or direct vasodilatation) may potentiate orthostatic hypotension.

Methyldopa: There have been isolated reports of haemolytic anaemia occurring with concomitant use of hydrochlorothiazide and methyldopa.

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 rehydrated before administration.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data on the use of aliskiren in pregnant women. Aliskiren was not teratogenic in rats or rabbits (see section 5.3). Other substances that act directly on the RAAS have been associated with serious foetal malformations and neonatal death when used during second and third trimesters. 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.

Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or pre-eclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.

Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

No specific clinical studies have been performed with this combination, therefore Sprimeo HCT should not be used during the first trimester of pregnancy or in women planning to become pregnant and is contraindicated during the second and third trimesters (see section 4.3). A switch to a suitable alternative treatment should be carried out in advance of a planned pregnancy. If pregnancy is detected during therapy, Sprimeo HCT should be discontinued as soon as possible.

Breast-feeding
It is not known whether aliskiren is excreted in human milk. Aliskiren was secreted in the milk of lactating rats.

Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit milk production.

The use of Sprimeo HCT during breast-feeding is not recommended. If Sprimeo HCT is used during breast-feeding, doses should be kept as low as possible.

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed. Sprimeo HCT is unlikely to affect the ability to drive and use machines. However, when driving vehicles or operating machinery it must be borne in mind that dizziness or drowsiness may occasionally occur when taking antihypertensive therapy.

4.8 Undesirable effects

Aliskiren/hydrochlorothiazide combination
The safety of Sprimeo HCT has been evaluated in 9 clinical trials with more than 3,900 patients, including over 700 treated for over 6 months, and 190 for over 1 year. The incidence of adverse reactions showed no association with gender, age, body mass index, race or ethnicity. Treatment with Sprimeo HCT had an overall incidence of adverse experiences at doses up to 300 mg/25 mg similar to placebo. Adverse reactions have generally been mild and transient in nature and have only infrequently required discontinuation of therapy. The most common adverse drug reaction observed with Sprimeo HCT is diarrhoea. The adverse drug reactions previously reported with one of the individual components of Sprimeo HCT (aliskiren and hydrochlorothiazide) and listed in the respective paragraphs on the individual components may occur with Sprimeo HCT.

The frequency of adverse reactions listed below is defined using the following convention: 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) and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Gastrointestinal disorders	
Common:	Diarrhoea

Diarrhoea: Diarrhoea is a dose-related adverse drug reaction for aliskiren. In controlled clinical trials, the incidence of diarrhoea in Sprimeo HCT-treated patients was 1.3% compared to 1.4% for aliskiren- or 1.9% for hydrochlorothiazide-treated patients.

Serum potassium: In a large placebo-controlled clinical trial, the opposite effects of aliskiren (150 mg or 300 mg) and hydrochlorothiazide (12.5 mg or 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 potassium to detect possible electrolyte imbalance should be performed in patients at risk at appropriate intervals (see sections 4.4 and 4.5).

Additional information on individual components
Other adverse reactions previously reported with one of the individual components may occur with Sprimeo HCT even if not observed in clinical trials.

Aliskiren
Treatment with Aliskiren up to 300 mg resulted in an overall incidence of adverse reactions similar to placebo. Adverse reactions have generally been mild and transient in nature and have only infrequently required discontinuation of therapy. The most common adverse drug reaction is diarrhoea.

The known aliskiren adverse drug reactions are presented in the table below using the same convention as described previously for the fixed combination.

Nervous system disorders		
	Common:	Dizziness
Vascular disorders		
	Uncommon:	Hypotension
Gastrointestinal disorders		
	Common:	Diarrhoea
Immune system disorders		
	Rare:	Hypersensitivity reactions
Skin and subcutaneous tissue disorders		
	Uncommon:	Rash, severe cutaneous adverse reactions (SCARs) including toxic epidermal necrolysis (TEN) and oral mucosal reactions
	Rare:	Angioedema
Musculoskeletal and connective tissue disorders		
	Common:	Arthralgia
Renal and urinary disorders		
	Uncommon:	Acute renal failure, renal impairment
General disorders and administration site conditions		
	Uncommon:	Oedema peripheral
Investigations		
	Common:	Hyperkalaemia
	Rare:	Haemoglobin decreased, haematocrit decreased
	Rare:	Blood creatinine increased

Angioedema and hypersensitivity reactions have occurred during treatment with aliskiren. In controlled clinical trials, angioedema and hypersensitivity reactions occurred rarely during treatment with aliskiren with rates comparable to treatment with placebo or comparators.

Cases of angioedema or symptoms suggestive of angioedema (swelling of the face, lips, throat and/or tongue) have also been reported in post-marketing experience. A number of these patients had a history of angioedema or symptoms suggestive of angioedema which in some cases was associated with the administration of other medicines known to cause angioedema, including RAAS blockers (ACE inhibitors or ARBs).

Hypersensitivity reactions have also been reported in post-marketing experience.

In the event of any signs suggesting a hypersensitivity reaction/angioedema (in particular difficulties in breathing or swallowing, rash, itching, hives or swelling of the face, extremities, eyes, lips and/or tongue, dizziness) patients should discontinue treatment and contact the physician (see section 4.4).

Arthralgia has been reported in post-marketing experience. In some cases this occurred as part of a hypersensitivity reaction.

Haemoglobin and haematocrit: Small decreases in haemoglobin and haematocrit (mean decreases of approximately 0.05 mmol/l and 0.16 volume percent, respectively) were observed. No patients discontinued therapy due to anaemia. This effect is also seen with other agents acting on the renin-angiotensin system, such as ACEI and ARBs.

Serum potassium: Increases in serum potassium have been observed with aliskiren and these may be exacerbated by concomitant use of other agents acting on the RAAS or by NSAIDs. Consistent with standard medical practice, periodic determination of renal function including serum electrolytes is advised if co-administration is considered necessary. The combination of aliskiren with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) and is not recommended in other patients (see sections 4.3, 4.4 and 5.1).

In post-marketing experience, renal dysfunction and cases of acute renal failure have been reported in patients at risk (see section 4.4). There have also been reports of peripheral oedema, increase in blood creatinine and severe cutaneous adverse reactions (SCARs) including toxic epidermal necrolysis (TEN) and oral mucosal reactions.

Hydrochlorothiazide
Hydrochlorothiazide has been extensively prescribed for many years, frequently in higher doses than those contained in Sprimeo HCT. The following adverse reactions have been reported in patients treated with thiazide diuretics alone, including hydrochlorothiazide:

Blood and lymphatic system disorders		
	Rare:	Thrombocytopenia sometimes with purpura
	Very rare:	Agranulocytosis, bone marrow depression, haemolytic anaemia, leucopenia
	Not known:	Aplastic anaemia
Immune system disorders		
	Very rare:	Hypersensitivity
Metabolism and nutrition disorders		
	Very common:	Hypokalaemia
	Common:	Hyperuricaemia, hypomagnesaemia, hyponatraemia
	Rare:	Hypercalcaemia, hyperglycaemia, worsening of diabetic metabolic state
	Very rare:	Hypochloraemic alkalosis
Psychiatric disorders		
	Rare:	Depression, sleep disturbances
Nervous system disorders		
	Rare:	Dizziness, headache, paraesthesia
Eye disorders		
	Rare:	Visual impairment
	Not known:	Acute angle-closure glaucoma
Cardiac disorders		
	Rare:	Cardiac arrhythmias
Vascular disorders		
	Common:	Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders		
	Very rare:	Respiratory distress (including pneumonitis and pulmonary oedema)
Gastrointestinal disorders		
	Common:	Decreased appetite, mild nausea and vomiting
	Rare:	Abdominal discomfort, constipation, diarrhoea
	Very rare:	Pancreatitis
Hepatobiliary disorders		
	Rare:	Intrahepatic cholestasis, jaundice
Skin and subcutaneous tissue disorders		
	Common:	Urticaria and other forms of rash
	Rare:	Photosensitivity reactions
	Very rare:	Cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, vasculitis necrotising and toxic epidermal necrolysis
	Not known:	Erythema multiforme
Musculoskeletal and connective tissue disorders		
	Not known:	Muscle spasm
Renal and urinary disorders		
	Not known:	Renal dysfunction, acute renal failure

Reproductive system and breast disorders		
	Common:	Impotence
General disorders and administration site conditions		
	Not known:	Asthenia, pyrexia
Investigations		
	Very common:	Increases in cholesterol and triglycerides
	Rare:	Glycosuria

4.9 Overdose

No information is available on the treatment of overdose with Sprimeo HCT. The most likely manifestation of overdose would be hypotension, related to the antihypertensive effect of aliskiren.

Overdose with hydrochlorothiazide is associated with electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration 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 cardiac arrhythmias associated with the concomitant use of digitalis glycosides or certain antiarrhythmic medicinal products. If symptomatic hypotension should occur, supportive treatment should be initiated.

In a study conducted in patients with end stage renal disease (ESRD) receiving haemodialysis, dialysis clearance of aliskiren was low (< 2% of oral clearance). Therefore dialysis is not adequate to treat aliskiren over-exposure.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Renin inhibitor (aliskiren) combinations with diuretics (hydrochlorothiazide), ATC code: C09XA52
Sprimeo HCT combines two antihypertensive compounds to control blood pressure in patients with essential hypertension: Aliskiren belongs to the class of direct renin inhibitors and hydrochlorothiazide to the class of thiazide diuretics. The combination of these substances with complementary mechanisms of action provides an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Aliskiren
Aliskiren is an orally active, non-peptide, potent and selective direct inhibitor of human renin.

By inhibiting the enzyme renin, aliskiren inhibits the RAAS at the point of activation, blocking the conversion of angiotensinogen to angiotensin I and decreasing levels of angiotensin I and angiotensin II. Whereas other agents that inhibit the RAAS (angiotensin converting enzyme inhibitors (ACEI) and angiotension II receptor blockers (ARB)) cause a compensatory rise in plasma renin activity (PRA), treatment with aliskiren decreases PRA in hypertensive patients by approximately 50 to 80%. Similar reductions were found when aliskiren was combined with other antihypertensive agents. The clinical implications of the effects on PRA are not known at the present time.

In hypertensive patients, once-daily administration of aliskiren at doses of 150 mg and 300 mg provided dose-dependent reductions in both systolic and diastolic blood pressure that were maintained over the entire 24-hour dose interval (maintaining benefit in the early morning) with a mean peak to trough ratio for diastolic response of up to 98% for the 300 mg dose. 85 to 90% of the maximal blood-pressure-lowering effect was observed after 2 weeks. The blood-pressure-lowering effect was sustained during long-term treatment (12 months), and was independent of age, gender, body mass index and ethnicity.

Combination therapy studies are available for aliskiren added to the diuretic hydrochlorothiazide, the calcium channel blocker amlodipine and the beta blocker atenolol. These combinations were efficacious and well tolerated.

The efficacy and safety of aliskiren-based therapy were compared to ramipril-based therapy in a 9-month non-inferiority study in 901 elderly patients (≥ 65 years) with essential systolic hypertension. Aliskiren 150 mg or 300 mg per day or ramipril 5 mg or 10 mg per day were administered for 36 weeks with optional add-on therapy of hydrochlorothiazide (12.5 mg or 25 mg) at week 12, and amlodipine (5 mg or 10 mg) at week 22. Over the 12 week period, aliskiren monotherapy lowered systolic/diastolic blood pressure by 14.0/5.1 mmHg, compared to 11.6/3.6 mmHg for ramipril, consistent with aliskiren being non-inferior to ramipril at the dosages chosen and the differences in systolic and diastolic blood pressure were statistically significant. Tolerability was comparable in both treatment arms, however cough was more often reported with the ramipril regimen than the aliskiren regimen (14.2% vs. 4.4%), whilst diarrhoea was more common with the aliskiren regimen than for the ramipril regimen (6.6% vs. 5.0%).

In a 8-week study in 754 hypertensive elderly (≥ 65 years) and very elderly patients (30% ≥ 75 years) aliskiren at doses of 75 mg, 150 mg and 300 mg provided statistically significant superior reduction in blood pressure (both systolic and diastolic) when compared to placebo. No additional blood pressure lowering effect was detected with 300 mg aliskiren compared to 150 mg aliskiren. All three doses were well tolerated in both elderly and very elderly patients.

There has been no evidence of first-dose hypotension and no effect on pulse rate in patients treated in controlled clinical studies. With cessation of treatment, blood pressure gradually returned towards baseline levels over a period of several weeks, with no evidence of a rebound effect for blood pressure or PRA.

In a 36-week study involving 820 patients with ischaemic left ventricular dysfunction, no changes in ventricular remodelling as assessed by left ventricular end systolic volume were detected with aliskiren compared to placebo on top of background therapy.

The combined rates of cardiovascular death, hospitalisation for heart failure, recurrent heart attack, stroke and resuscitated sudden death were similar in the aliskiren group and the placebo group. However, in patients receiving aliskiren there was a significantly higher rate of hyperkalaemia, hypotension and kidney dysfunction when compared to the placebo group.

Aliskiren was evaluated for cardiovascular and/or renal benefit in a double-blind placebo controlled randomised trial in 8,606 patients with type 2 diabetes and chronic kidney disease (evidenced by proteinuria and/or GFR < 60 ml/min/1.73 m^2) with or without cardiovascular disease. In most patients arterial blood pressure was well controlled at baseline. The primary endpoint was a composite of cardiovascular and renal complications.

In this study, aliskiren 300 mg was compared to placebo when added to standard of care which included either an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker. The study was discontinued prematurely because the participants were unlikely to benefit from aliskiren. Preliminary study results indicated a hazard ratio for the primary endpoint of 1.09 in favour of placebo (95% Confidence Interval: 0.97, 1.22, 2-sided p=0.17). In addition, an increased incidence of serious adverse outcomes was observed with aliskiren compared to placebo for renal complications (4.7% versus 3.3%), hyperkalaemia (36.9% versus 27.1%), hypotension (18.4% versus 14.6%) and stroke (2.7% versus 2.0%). The increased incidence of non-fatal stroke was greater in patients with renal insufficiency.

Hydrochlorothiazide
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 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.

Aliskiren/hydrochlorothiazide
Over 3,900 hypertensive patients received Sprimeo HCT once daily in clinical trials.

In hypertensive patients, once-daily administration of Sprimeo HCT provided dose-dependent reductions in both systolic and diastolic blood pressure that were maintained over the entire 24-hour dose interval. The antihypertensive effect is largely manifested within 1 week and the maximum effect is generally seen within 4 weeks.The blood-pressure-lowering effect was sustained during long-term treatment, and was independent of age, gender, body mass index and ethnicity. The antihypertensive effect of a single dose of the combination persisted for 24 hours. Upon withdrawal of the aliskiren treatment (aliskiren with or without hydrochlorothiazide add-on), the return of blood pressure towards baseline was gradual (3-4 weeks) with no evidence of the rebound effect.

Sprimeo HCT was studied in a placebo-controlled trial including 2,762 hypertensive patients with diastolic blood pressure ≥ 95 mmHg and < 110 mmHg (mean baseline blood pressure of 153.6/99.2 mmHg). In this study, Sprimeo HCT in doses from 150 mg/12.5 mg to 300 mg/25 mg produced dose-dependent blood pressure reductions (systolic/diastolic) from 17.6/11.9 mmHg to 21.2/14.3 mmHg, respectively, compared to 7.5/6.9 mmHg with placebo. The greater blood pressure reductions with these combination doses were also significantly greater than the respective doses of aliskiren and hydrochlorothiazide when used alone. The combination of aliskiren and hydrochlorothiazide neutralised the reactive increase of PRA caused by hydrochlorothiazide.

When administered in hypertensive patients with markedly elevated blood pressure (systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 100 mmHg), Sprimeo HCT in doses from 150 mg/12.5 mg to 300 mg/25 mg administered without up-titration from monotherapy demonstrated significantly greater systolic/diastolic blood pressure control rates (< 140/90 mmHg) as compared to the respective monotherapies. In this population, Sprimeo HCT 150 mg/12.5 mg to 300 mg/25 mg provided dose-dependent systolic/diastolic blood pressure reduction from 20.6/12.4 mmHg to 24.8/14.5 mmHg, which were significantly superior to the respective monotherapies. The safety of the combination therapy was similar to the respective monotherapies regardless of severity of hypertension or of the presence or absence of additional cardiovascular risk. Hypotension and related adverse events were uncommon with the combination treatment, with no increased incidence in elderly patients.

In a study in 880 randomised patients not adequately responsive to aliskiren 300 mg treatment, the combination of aliskiren/hydrochlorothiazide 300 mg/25 mg produced systolic/diastolic blood pressure reductions of 15.8/11.0 mmHg, which were significantly greater than aliskiren 300 mg monotherapy. In a study in 722 randomised patients not adequately responsive to hydrochlorothiazide 25 mg treatment, the combination of aliskiren/hydrochlorothiazide 300 mg/25 mg produced systolic/diastolic blood pressure reductions of 16.78/10.7 mmHg, which were significantly greater than hydrochlorothiazide 25 mg monotherapy.

In another clinical trial, the efficacy and safety of Sprimeo HCT were also assessed in 489 obese hypertensive patients who did not respond to hydrochlorothiazide 25 mg (baseline systolic/diastolic blood pressure 149.4/96.8 mmHg). In this difficult-to-treat population, Sprimeo HCT provided a blood pressure reduction (systolic/diastolic) of 15.8/11.9 mmHg compared to 15.4/11.3 mmHg for irbesartan/hydrochlorothiazide, 13.6/10.3 mmHg for amlodipine/hydrochlorothiazide and 8.6/7.9 mmHg for hydrochlorothiazide monotherapy, with similar safety to hydrochlorothiazide monotherapy.

In a study in 183 randomised patients with severe hypertension (mean sitting diastolic blood pressure ≥ 105 and < 120 mmHg), aliskiren treatment regimen with optional addition of hydrochlorothiazide 25 mg was shown to be safe and efficacious in reducing blood pressure.

5.2 Pharmacokinetic properties

Aliskiren

Absorption

Following oral absorption, peak plasma concentrations of aliskiren are reached after 1-3 hours. The absolute bioavailability of aliskiren is approximately 2-3%. Meals with a high fat content reduce C_{max} by 85% and AUC by 70%. Steady-state-plasma concentrations are reached within 5-7 days following once-daily administration and steady-state levels are approximately 2-fold greater than with the initial dose.

Distribution

Following intravenous administration, the mean volume of distribution at steady state is approximately 135 litres, indicating that aliskiren distributes extensively into the extravascular space. Aliskiren plasma protein binding is moderate (47-51%) and independent of the concentration.

Metabolism and elimination

The mean half-life is about 40 hours (range 34-41 hours). Aliskiren is mainly eliminated as unchanged compound in the faeces (oral radioactive dose recovery = 91%). Approximately 1.4% of the total oral dose is metabolised. The enzyme responsible for this metabolism is CYP3A4. Approximately 0.6% of the dose is recovered in urine following oral administration. Following intravenous administration, the mean plasma clearance is approximately 9 l/h.

Linearity

Exposure to aliskiren increased slightly more than in proportion to the increase in dose. After single dose administration in the dose range of 75 to 600 mg, a 2-fold increase in dose results in a ~2.3 and 2.6-fold increase in AUC and C_{max}, respectively. Mechanisms responsible for the deviation from dose proportionality have not been identified. A possible mechanism is saturation of transporters at the absorption site or at the hepatobiliary clearance route.

Hydrochlorothiazide

Absorption

The absorption of hydrochlorothiazide, after an oral dose, is rapid (T_{max} about 2 h). 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.

Metabolism and elimination
Hydrochlorothiazide is eliminated predominantly as unchanged compound. 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. There is more than 95% of the absorbed dose being excreted as unchanged compound in the urine. The renal clearance is composed of passive filtration and active secretion into the renal tubule.

Aliskiren/hydrochlorothiazide
Following oral administration of Sprimeo HCT tablets, the median peak plasma concentration time is within 1 hour for aliskiren and 2.5 hours for hydrochlorothiazide.

The rate and extent of absorption of Sprimeo HCT are equivalent to the bioavailability of aliskiren and hydrochlorothiazide when administered as individual monotherapies. Similar food effect was observed for Sprimeo HCT as for the individual monotherapies.

Characteristics in patients
Sprimeo HCT has been shown to be effective as a once-a-day antihypertensive treatment in adult patients, regardless of gender, age, body mass index and ethnicity.

The pharmacokinetics of aliskiren are not significantly affected in patients with mild to moderate liver disease. Consequently, no initial dose adjustment of Sprimeo HCT is required in patients with mild to moderate hepatic impairment. No data are available on patients with severe hepatic impairment treated by Sprimeo HCT. Sprimeo HCT is contraindicated in patients with severe hepatic impairment (see section 4.3).

No adjustment of the initial dose is required for patients with mild to moderate renal impairment (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. Sprimeo HCT is contraindicated in patients with anuria or severe renal impairment (GFR < 30 ml/min/1.73 m^2) and the concomitant use of Sprimeo HCT with ARBs or ACEIs is contraindicated in patients with renal impairment (GFR < 60 ml/min/1.73 m^2) (see section 4.3).

The pharmacokinetics of aliskiren were evaluated in patients with end stage renal disease receiving haemodialysis. Administration of a single oral dose of 300 mg aliskiren was associated with very minor changes in the pharmacokinetics of aliskiren (change in C_{max} of less than 1.2 fold; increase in AUC of up to 1.6 fold) compared to matched healthy subjects. Timing of haemodialysis did not significantly alter the pharmacokinetics of aliskiren in ESRD patients. Therefore, if administration of aliskiren in ESRD patients receiving haemodialysis is considered necessary, no dose adjustment is warranted in these patients. However, the use of aliskiren is not recommended in patients with severe renal impairment (see section 4.4).

No initial dose adjustment of Sprimeo HCT is required in elderly patients. Limited data suggest that the systemic clearance of hydrochlorothiazide is reduced in both healthy and hypertensive elderly subjects compared to young healthy volunteers.

No pharmacokinetic data are available in the paediatric population.

5.3 Preclinical safety data

Safety pharmacology studies with aliskiren did not reveal any adverse effects on central nervous, respiratory or cardiovascular function. Findings during repeat-dose toxicity studies in animals were consistent with the known local irritation potential or the expected pharmacological effects of aliskiren. No carcinogenic potential for aliskiren was detected in a 2-year rat study and a 6-month transgenic mouse study. One colonic adenoma and one caecal adenocarcinoma recorded in rats at the dose of 1,500 mg/kg/day were not statistically significant. Aliskiren was devoid of any mutagenic potential, embryo-foetal toxicity or teratogenicity. Fertility, prenatal development and postnatal development were unaffected in rats.

Preclinical evaluations to support the administration of hydrochlorothiazide in humans included *in vitro* genotoxicity assays and reproductive toxicity and carcinogenicity studies in rodents. Extensive clinical data are available for hydrochlorothiazide and these are reflected in the relevant sections.

The findings observed in the 2-week and 13-week toxicity studies were consistent with those observed previously with aliskiren or hydrochlorothiazide monotherapies. There were no new or unexpected findings observed of relevance to human use. Increased cellular vacuolation of the adrenal gland zona glomerulosa was observed during the 13-week toxicity study in rats. The finding was observed in animals treated with hydrochlorothiazide but not in those animals receiving aliskiren alone or vehicle. There was no evidence that this finding was enhanced in the aliskiren/hydrochlorothiazide combination as it was only apparent at a minimal severity in all animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Cellulose microcrystalline
Crospovidone
Lactose monohydrate
Wheat starch
Povidone
Magnesium stearate
Silica colloidal anhydrous
Talc

Coating:
Talc
Hypromellose
Macrogol
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

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

PA/Alu/PVC – Alu blisters:
Single-packs containing 7, 14, 28, 30, 50 or 56 tablets.
Multi-packs containing 90, 98 or 280 tablets.

PVC/polychlorotrifluoroethylene (PCTFE) – Alu blisters:
Single-packs containing 7, 14, 28, 30, 50, 56, 90 or 98 tablets.
Single-packs (perforated unit dose blister) containing 56 x 1 tablets.
Multi-packs containing 280 tablets.
Multi-packs (perforated unit dose blister) containing 98 x 1 tablets.

Not all pack sizes or strengths may be marketed.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/683/001-020

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23.06.2011

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Sprimeo HCT 150 mg/25 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 150 mg aliskiren (as hemifumarate) and 25 mg hydrochlorothiazide.

Excipients: Each tablet contains 50 mg lactose monohydrate and 49 mg wheat starch.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Pale yellow, biconvex, ovaloid film-coated tablet imprinted with “CLL” on one side and “NVR” on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension in adults.

Sprimeo HCT is indicated in patients whose blood pressure is not adequately controlled on aliskiren or hydrochlorothiazide used alone.

Sprimeo HCT is indicated as substitution therapy in patients adequately controlled with aliskiren and hydrochlorothiazide, given concurrently, at the same dose level as in the combination.

4.2 Posology and method of administration

The recommended dose of Sprimeo HCT is one tablet per day. Sprimeo HCT should be taken with a light meal once a day, preferably at the same time each day. Grapefruit juice should not be taken together with Sprimeo HCT.

The antihypertensive effect is largely manifested within 1 week and the maximum effect is generally seen within 4 weeks.

Posology in patients not adequately controlled with aliskiren or hydrochlorothiazide monotherapy
Individual dose titration with each of the two components may be recommended before changing to the fixed combination. When clinically appropriate, direct change from monotherapy to the fixed combination may be considered.

Sprimeo HCT 150 mg /25 mg may be administered in patients whose blood pressure is not adequately controlled with aliskiren 150 mg or hydrochlorothiazide 25 mg alone or by Sprimeo HCT 150 mg/12.5 mg.

If blood pressure remains uncontrolled after 2-4 weeks of therapy, the dose may be titrated up to a maximum of Sprimeo HCT 300 mg/25 mg daily. Dosing should be individualised and adjusted according to the patient’s clinical response.

Posology as substitution therapy
For convenience, patients receiving aliskiren and hydrochlorothiazide from separate tablets may be switched to a fixed combination tablet of Sprimeo HCT containing the same component doses.

Renal impairment
No adjustment of the initial dose is required for patients with mild to moderate renal impairment (see sections 4.4 and 5.2). Due to the hydrochlorothiazide component, Sprimeo HCT is contraindicated for use in patients with anuria and in patients with severe renal impairment (glomerular filtration rate (GFR) < 30 ml/min/1.73 m^2). The concomitant use of Sprimeo HCT with angiotensin II receptor blockers (ARB) or angiotensin converting enzyme inhibitors (ACEI) is contraindicated in patients with renal impairment (GFR < 60 ml/min/1.73 m^2) (see sections 4.3, 4.4 and 5.2).

Hepatic impairment
No adjustment of the initial dose is required for patients with mild to moderate hepatic impairment (see section 5.2). Sprimeo HCT is contraindicated in patients with severe hepatic impairment (see sections 4.3 and 4.4).

Elderly patients (over 65 years)
The recommended starting dose of aliskiren in elderly patients is 150 mg. No clinically meaningful additional blood pressure reduction is observed by increasing the dose to 300 mg in the majority of elderly patients.

Paediatric patients
Sprimeo HCT is not recommended for use in children and adolescents below age 18 due to a lack of data on safety and efficacy (see section 5.2).

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients (see section 6.1), or to other sulphonamide-derived substances.
- History of angioedema with aliskiren.
- Hereditary or idiopathic angioedema.
- Second and third trimesters of pregnancy (see section 4.6).
- Anuria.
- Severe renal impairment (GFR < 30 ml/min/1.73 m^2).
- Refractory hypokalaemia, hyponatraemia, hypercalcaemia and symptomatic hyperuricaemia.
- Severe hepatic impairment.
- The concomitant use of aliskiren with ciclosporin and itraconazole, two highly potent P-glycoprotein (P-gp) inhibitors, and other potent P-gp inhibitors (e.g. quinidine), is contraindicated (see section 4.5).
- The concomitant use of aliskiren with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) (see sections 4.2, 4.4, 4.5 and 5.1).

4.4 Special warnings and precautions for use

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
Hypotension, syncope, stroke, hyperkalaemia, and changes in renal function (including acute renal failure) have been reported in susceptible individuals, especially if combining medicinal products that affect this system (see section 5.1). Dual blockade of the renin-angiotensin-aldosterone system by combining aliskiren with an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin II receptor blocker (ARB) is therefore not recommended.

The use of aliskiren in combination with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) (see section 4.3).

Heart failure
Aliskiren should be used with caution in patients with serious congestive heart failure (New York Heart Association (NYHA) functional class III-IV). Sprimeo HCT should be used with caution in patients with heart failure due to limited clinical efficacy and safety data.

Angioedema
As with other agents acting on the renin-angiotensin system, angioedema or symptoms suggestive of angioedema (swelling of the face, lips, throat and/or tongue) have been reported in patients treated with aliskiren.

A number of these patients had a history of angioedema or symptoms suggestive of angioedema, which in some cases followed use of other medicines that can cause angioedema, including RAAS blockers (angiotensin converting enzyme inhibitors or angiotensin receptor blockers) (see section 4.8).

Patients with a history of angioedema may be at increased risk of experiencing angioedema during treatment with aliskiren (see sections 4.3 and 4.8). Caution should therefore be exercised when prescribing aliskiren to patients with a history of angioedema, and such patients should be closely monitored during treatment (see section 4.8) especially at the beginning of the treatment.

If angioedema occurs, Sprimeo HCT should be promptly discontinued and appropriate therapy and monitoring provided until complete and sustained resolution of signs and symptoms has occurred. Where there is involvement of the tongue, glottis or larynx adrenaline should be administered. In addition, measures necessary to maintain patent airways should be provided.

Sodium- and/or volume-depleted patients
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 Sprimeo HCT. Sprimeo HCT should be used only after correction of any pre-existing sodium and/or volume depletion.

Electrolyte imbalance
Treatment with Sprimeo 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 Sprimeo HCT should be discontinued until stable correction of the potassium balance. Although hypokalaemia may develop with the use of thiazide diuretics, concurrent therapy with aliskiren may reduce diuretic-induced hypokalaemia. The risk of hypokalaemia is greater in patients with cirrhosis of the liver, patients experiencing brisk diuresis, patients with inadequate oral electrolyte intake and patients receiving concomitant therapy with corticosteroids or adrenocorticotropic hormone (ACTH) (see sections 4.5 and 4.8).

Conversely, increases in serum potassium have been observed with aliskiren in post-marketing experience and these may be exacerbated by concomitant use of other agents acting on the RAAS or by non-steroidal anti-inflammatory drugs (NSAIDs). Consistent with standard medical practice, periodic determination of renal function including serum electrolytes is advised if co-administration is considered necessary. The concomitant use of aliskiren and ACEIs or ARBs is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) (see sections 4.3, 4.5 and 4.8).

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 Sprimeo HCT therapy, the treatment should be discontinued until normalisation of natraemia.

There is no evidence that Sprimeo HCT would reduce or prevent diuretic-induced hyponatraemia. Chloride deficit is generally mild and usually does not require treatment.

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

Thiazides reduce urinary calcium excretion and may cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Sprimeo HCT is contraindicated in patients with hypercalcaemia and should only be used after correction of any pre-existing hypercalcaemia. Sprimeo 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.

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

No dosage adjustment is necessary in patients with mild to moderate renal impairment (GFR $\geq$ 30 ml/min/1.73 m^2).

There is no experience regarding the administration of Sprimeo HCT in patients who have recently undergone kidney transplantation.

As for other agents acting on the renin-angiotensin system, caution should be exercised when aliskiren is given in the presence of conditions pre-disposing to kidney dysfunction such as hypovolaemia (e.g. due to blood loss, severe or prolonged diarrhoea, prolonged vomiting, etc.), heart disease, liver disease, diabetes mellitus or kidney disease. The concomitant use of aliskiren and ACEIs or ARBs is contraindicated in patients with renal impairment (GFR < 60 ml/min/1.73 m^2). Acute renal failure, reversible upon discontinuation of treatment, has been reported in at-risk patients receiving aliskiren in post-marketing experience. In the event that any signs of renal failure occur, aliskiren should be promptly discontinued.

Hepatic impairment
Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. No adjustment of the initial dose is required for patients with mild to moderate hepatic impairment. No data are available for the use of Sprimeo HCT in patients with severe hepatic impairment. Due to the hydrochlorothiazide component, Sprimeo HCT is contraindicated in patients with severe hepatic impairment (see sections 4.3 and 5.2).

There is no clinical experience with Sprimeo HCT in patients with hepatic impairment.

Moderate P-gp inhibitors
Co-administration of aliskiren 300 mg with ketoconazole 200 mg or verapamil 240 mg resulted in a 76% or 97% increase in aliskiren AUC, respectively. Therefore caution should be exercised when aliskiren is administered with moderate P-gp inhibitors such as ketoconazole or verapamil (see section 4.5).

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy
As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Renal artery stenosis and renovascular hypertension
No controlled clinical data are available on the use of Sprimeo HCT in patients with unilateral or bilateral renal artery stenosis, or stenosis to a solitary kidney. However, as with other agents acting on the renin-angiotensin system, there is an increased risk of renal insufficiency, including acute renal failure, when patients with renal artery stenosis are treated with aliskiren. Therefore caution should be exercised in these patients. If renal failure occurs, treatment should be discontinued.

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

Metabolic and endocrine effects
Thiazide diuretics, including hydrochlorothiazide, may alter glucose tolerance and raise serum levels of cholesterol and triglycerides, and uric acid. In diabetic patients dosage adjustments of insulin or oral hypoglycaemic agents may be required. Concomitant use of Sprimeo HCT with ARBs or ACEIs is contraindicated in patients with diabetes mellitus (see section 4.3).

Due to the hydrochlorothiazide component, Sprimeo HCT is contraindicated in symptomatic hyperuricaemia (see section 4.3). 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 an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Sprimeo HCT is contraindicated in patients with hypercalcaemia and should only be used after correction of any pre-existing hypercalcaemia. Sprimeo 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 Sprimeo HCT, it is recommended to stop the treatment. If a re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Acute angle-closure glaucoma
Hydrochlorothiazide, a sulphonamide, has been associated with an idiosyncratic reaction resulting in 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 weeks 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
In the event of severe and persistent diarrhoea, Sprimeo HCT therapy should be stopped.

As with any antihypertensive agent, excessive reduction of blood pressure in patients with ischaemic cardiopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke.

Hypersensitivity reactions to hydrochlorothiazide may occur in patients, but are more likely in patients with allergy and asthma.

Excipients
Sprimeo HCT contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sprimeo HCT contains wheat starch. It is suitable for people with coeliac disease. Patients with wheat allergy (different from coeliac disease) should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Information on Sprimeo HCT interactions
Medicinal products affecting serum potassium levels: The potassium-depleting effect of hydrochlorothiazide is attenuated by the potassium-sparing effect of aliskiren. However, this effect of hydrochlorothiazide on serum potassium would be expected to be potentiated by other medicinal products associated with potassium loss and hypokalaemia (e.g. other kaliuretic diuretics, corticosteroids, laxatives, adrenocorticotropic hormone (ACTH), amphotericin, carbenoxolone, penicillin G, salicylic acid derivatives). Conversely, concomitant use of other agents affecting the RAAS, of NSAIDs or of agents that increase serum potassium levels (e.g. potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, heparin) may lead to increases in serum potassium. If co-medication with an agent affecting the level of serum potassium is considered necessary, caution is advisable. The combination of aliskiren with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) and is not recommended in other patients (see sections 4.3, 4.4 and 5.1).

Medicinal products affected by serum potassium disturbances: Periodic monitoring of serum potassium is recommended when Sprimeo HCT is administered with medicinal products affected by serum potassium disturbances (e.g. digitalis glycosides, antiarrhythmics).

Non-steroidal anti-inflammatory drugs (NSAIDs), including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors), acetylsalicylic acid and non-selective NSAIDs: As with other agents acting on the renin-angiotensin system, NSAIDs may reduce the anti-hypertensive effect of aliskiren. NSAIDs may also weaken the diuretic and antihypertensive activity of hydrochlorothiazide.

In some patients with compromised renal function (dehydrated patients or elderly patients) aliskiren and hydrochlorothiazide given concomitantly with NSAIDs may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore the use of Sprimeo HCT with an NSAID requires caution, especially in elderly patients.

Other antihypertensive agents: The antihypertensive effect of Sprimeo HCT may be increased with the concomitant use of other antihypertensive agents.

Additional information on aliskiren interactions
The combination of aliskiren with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) and is not recommended in other patients (see sections 4.3, 4.4 and 5.1).

Compounds that have been investigated in aliskiren clinical pharmacokinetic studies include acenocoumarol, atenolol, celecoxib, fenofibrate, pioglitazone, allopurinol, isosorbide-5-mononitrate, digoxin, metformin, amlodipine, atorvastatin, cimetidine and hydrochlorothiazide. No clinically relevant interactions have been identified. As a result no dose adjustment for aliskiren or these co-administered medicinal products is necessary.

P-glycoprotein interactions: MDR1/Mdr1a/1b (P-gp) was found to be the major efflux system involved in intestinal absorption and biliary excretion of aliskiren in preclinical studies. Rifampicin, which is an inducer of P-gp, reduced aliskiren bioavailability by approximately 50% in a clinical study. Other inducers of P-gp (St. John's wort) might decrease the bioavailability of aliskiren. Although this has not been investigated for aliskiren, it is known that P-gp also controls tissue uptake of a variety of substrates and P-gp inhibitors can increase the tissue-to-plasma concentration ratios. Therefore, P-gp inhibitors may increase tissue levels more than plasma levels. The potential for drug interactions at the P-gp site will likely depend on the degree of inhibition of this transporter.

P-gp potent inhibitors: A single dose drug interaction study in healthy subjects has shown that ciclosporin (200 and 600 mg) increases C_{max} of aliskiren 75 mg approximately 2.5-fold and AUC approximately 5-fold. The increase may be higher with higher aliskiren doses. In healthy subjects, itraconazole (100 mg) increases AUC and C_{max} of aliskiren (150 mg) by 6.5-fold and 5.8-fold, respectively. Therefore, concomitant use of aliskiren and P-gp potent inhibitors is contraindicated (see section 4.3).

Moderate P-gp inhibitors: Co-administration of ketoconazole (200 mg) or verapamil (240 mg) with aliskiren (300 mg) resulted in a 76% or 97% increase in aliskiren AUC, respectively. The change in plasma levels of aliskiren in the presence of ketoconazole or verapamil is expected to be within the range that would be achieved if the dose of aliskiren were doubled; aliskiren doses of up to 600 mg, or twice the highest recommended therapeutic dose, have been found to be well tolerated in controlled clinical trials. Preclinical studies indicate that aliskiren and ketoconazole co-administration enhances aliskiren gastrointestinal absorption and decreases biliary excretion. Therefore, caution should be exercised when aliskiren is administered with ketoconazole, verapamil or other moderate P-gp inhibitors (clarithromycin, telithromycin, erythromycin, amiodarone).

P-gp substrates or weak inhibitors: No relevant interactions with atenolol, digoxin, amlodipine or cimetidine have been observed. When administered with atorvastatin (80 mg), steady-state aliskiren (300 mg) AUC and C_{max} increased by 50%.

Organic anion transporting polypeptide (OATP) inhibitors: Preclinical studies indicate that aliskiren might be a substrate of organic anion transporting polypeptides. Therefore, the potential exists for interactions between OATP inhibitors and aliskiren when administered concomitantly (see interaction with Grapefruit juice).

Grapefruit juice: Administration of grapefruit juice with aliskiren resulted in a decrease in AUC and C_{max} of aliskiren. Co-administration with aliskiren 150 mg resulted in a 61% decrease in aliskiren AUC and co-administration with aliskiren 300 mg resulted in a 38% decrease in aliskiren AUC. This decrease is likely due to an inhibition of organic anion transporting polypeptide-mediated uptake of aliskiren by grapefruit juice in the gastrointestinal tract. Therefore, because of the risk of therapeutic failure, grapefruit juice should not be taken together with Sprimeo HCT.

Furosemide: When aliskiren was co-administered with furosemide, the AUC and C_{max} of furosemide were reduced by 28% and 49%, respectively. It is therefore recommended to monitor the effects when initiating and adjusting furosemide therapy to avoid possible underutilisation in clinical situations of volume overload.

Warfarin: The effects of aliskiren on warfarin pharmacokinetics have not been evaluated.

Food interactions: Meals with a high fat content have been shown to reduce the absorption of aliskiren substantially.

Additional information on hydrochlorothiazide interactions
When administered concurrently, the following medicinal products may interact with thiazide diuretics:

Lithium: Renal clearance of lithium is reduced by thiazides, therefore the risk of lithium toxicity may be increased with hydrochlorothiazide. Co-administration of lithium and hydrochlorothiazide is not recommended. If this combination proves essential, careful monitoring of serum lithium level is recommended during concomitant use.

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 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.

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.

Digoxine or other digitalis glycosides: Thiazide-induced hypokalaemia or hypomagnesaemia may occur as undesirable effects, favouring the onset of digitalis-induced cardiac arrhythmias.

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.

Antidiabetic agents (e.g. insulin and oral antidiabetic agents): Thiazides may alter glucose tolerance. Dose adjustment of the antidiabetic medicinal product may be necessary (see section 4.4). 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.

Medicinal products used in the treatment of gout: 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.

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.

Amantadine: Thiazides, including hydrochlorothiazide, may increase the risk of adverse reactions caused by amantadine.

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.

Cytotoxic agents: Thiazides, including hydrochlorothiazide, may reduce the renal excretion of cytotoxic agents (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.

Non-depolarising skeletal muscle relaxants: Thiazides, including hydrochlorothiazide, potentiate the action of skeletal muscle relaxants such as curare derivatives.

Alcohol, barbiturates or narcotics: Concomitant administration of thiazide diuretics with subtances that also have a blood pressure lowering effect (e.g. by reducing sympathetic central nervous system activity or direct vasodilatation) may potentiate orthostatic hypotension.

Methyldopa: There have been isolated reports of haemolytic anaemia occurring with concomitant use of hydrochlorothiazide and methyldopa.

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 rehydrated before administration.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data on the use of aliskiren in pregnant women. Aliskiren was not teratogenic in rats or rabbits (see section 5.3). Other substances that act directly on the RAAS have been associated with serious foetal malformations and neonatal death when used during second and third trimesters. 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.

Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or pre-eclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.

Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

No specific clinical studies have been performed with this combination, therefore Sprimeo HCT should not be used during the first trimester of pregnancy or in women planning to become pregnant and is contraindicated during the second and third trimesters (see section 4.3). A switch to a suitable alternative treatment should be carried out in advance of a planned pregnancy. If pregnancy is detected during therapy, Sprimeo HCT should be discontinued as soon as possible.

Breast-feeding
It is not known whether aliskiren is excreted in human milk. Aliskiren was secreted in the milk of lactating rats.

Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit milk production.

The use of Sprimeo HCT during breast-feeding is not recommended. If Sprimeo HCT is used during breast-feeding, doses should be kept as low as possible.

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed. Sprimeo HCT is unlikely to affect the ability to drive and use machines. However, when driving vehicles or operating machinery it must be borne in mind that dizziness or drowsiness may occasionally occur when taking antihypertensive therapy.

4.8 Undesirable effects

Aliskiren/hydrochlorothiazide combination
The safety of Sprimeo HCT has been evaluated in 9 clinical trials with more than 3,900 patients, including over 700 treated for over 6 months, and 190 for over 1 year. The incidence of adverse reactions showed no association with gender, age, body mass index, race or ethnicity. Treatment with Sprimeo HCT had an overall incidence of adverse experiences at doses up to 300 mg/25 mg similar to placebo. Adverse reactions have generally been mild and transient in nature and have only infrequently required discontinuation of therapy. The most common adverse drug reaction observed with Sprimeo HCT is diarrhoea. The adverse drug reactions previously reported with one of the individual components of Sprimeo HCT (aliskiren and hydrochlorothiazide) and listed in the respective paragraphs on the individual components may occur with Sprimeo HCT.

The frequency of adverse reactions listed below is defined using the following convention: 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) and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Gastrointestinal disorders	
Common:	Diarrhoea

Diarrhoea: Diarrhoea is a dose-related adverse drug reaction for aliskiren. In controlled clinical trials, the incidence of diarrhoea in Sprimeo HCT-treated patients was 1.3% compared to 1.4% for aliskiren- or 1.9% for hydrochlorothiazide-treated patients.

Serum potassium: In a large placebo-controlled clinical trial, the opposite effects of aliskiren (150 mg or 300 mg) and hydrochlorothiazide (12.5 mg or 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 potassium to detect possible electrolyte imbalance should be performed in patients at risk at appropriate intervals (see sections 4.4 and 4.5).

Additional information on individual components
Other adverse reactions previously reported with one of the individual components may occur with Sprimeo HCT even if not observed in clinical trials.

Aliskiren
Treatment with Aliskiren up to 300 mg resulted in an overall incidence of adverse reactions similar to placebo. Adverse reactions have generally been mild and transient in nature and have only infrequently required discontinuation of therapy. The most common adverse drug reaction is diarrhoea.

The known aliskiren adverse drug reactions are presented in the table below using the same convention as described previously for the fixed combination.

Nervous system disorders		
	Common:	Dizziness
Vascular disorders		
	Uncommon:	Hypotension
Gastrointestinal disorders		
	Common:	Diarrhoea
Immune system disorders		
	Rare:	Hypersensitivity reactions
Skin and subcutaneous tissue disorders		
	Uncommon:	Rash, severe cutaneous adverse reactions (SCARs) including toxic epidermal necrolysis (TEN) and oral mucosal reactions
	Rare:	Angioedema
Musculoskeletal and connective tissue disorders		
	Common:	Arthralgia
Renal and urinary disorders		
	Uncommon:	Acute renal failure, renal impairment
General disorders and administration site conditions		
	Uncommon:	Oedema peripheral
Investigations		
	Common:	Hyperkalaemia
	Rare:	Haemoglobin decreased, haematocrit decreased
	Rare:	Blood creatinine increased

Angioedema and hypersensitivity reactions have occurred during treatment with aliskiren. In controlled clinical trials, angioedema and hypersensitivity reactions occurred rarely during treatment with aliskiren with rates comparable to treatment with placebo or comparators.

Cases of angioedema or symptoms suggestive of angioedema (swelling of the face, lips, throat and/or tongue) have also been reported in post-marketing experience. A number of these patients had a history of angioedema or symptoms suggestive of angioedema which in some cases was associated with the administration of other medicines known to cause angioedema, including RAAS blockers (ACE inhibitors or ARBs).

Hypersensitivity reactions have also been reported in post-marketing experience.

In the event of any signs suggesting a hypersensitivity reaction/angioedema (in particular difficulties in breathing or swallowing, rash, itching, hives or swelling of the face, extremities, eyes, lips and/or tongue, dizziness) patients should discontinue treatment and contact the physician (see section 4.4).

Arthralgia has been reported in post-marketing experience. In some cases this occurred as part of a hypersensitivity reaction.

Haemoglobin and haematocrit: Small decreases in haemoglobin and haematocrit (mean decreases of approximately 0.05 mmol/l and 0.16 volume percent, respectively) were observed. No patients discontinued therapy due to anaemia. This effect is also seen with other agents acting on the renin-angiotensin system, such as ACEI and ARBs.

Serum potassium: Increases in serum potassium have been observed with aliskiren and these may be exacerbated by concomitant use of other agents acting on the RAAS or by NSAIDs. Consistent with standard medical practice, periodic determination of renal function including serum electrolytes is advised if co-administration is considered necessary. The combination of aliskiren with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) and is not recommended in other patients (see sections 4.3, 4.4 and 5.1).

In post-marketing experience, renal dysfunction and cases of acute renal failure have been reported in patients at risk (see section 4.4). There have also been reports of peripheral oedema, increase in blood creatinine and severe cutaneous adverse reactions (SCARs) including toxic epidermal necrolysis (TEN) and oral mucosal reactions.

Hydrochlorothiazide
Hydrochlorothiazide has been extensively prescribed for many years, frequently in higher doses than those contained in Sprimeo HCT. The following adverse reactions have been reported in patients treated with thiazide diuretics alone, including hydrochlorothiazide:

Blood and lymphatic system disorders		
	Rare:	Thrombocytopenia sometimes with purpura
	Very rare:	Agranulocytosis, bone marrow depression, haemolytic anaemia, leucopenia
	Not known:	Aplastic anaemia
Immune system disorders		
	Very rare:	Hypersensitivity
Metabolism and nutrition disorders		
	Very common:	Hypokalaemia
	Common:	Hyperuricaemia, hypomagnesaemia, hyponatraemia
	Rare:	Hypercalcaemia, hyperglycaemia, worsening of diabetic metabolic state
	Very rare:	Hypochloraemic alkalosis
Psychiatric disorders		
	Rare:	Depression, sleep disturbances
Nervous system disorders		
	Rare:	Dizziness, headache, paraesthesia
Eye disorders		
	Rare:	Visual impairment
	Not known:	Acute angle-closure glaucoma
Cardiac disorders		
	Rare:	Cardiac arrhythmias
Vascular disorders		
	Common:	Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders		
	Very rare:	Respiratory distress (including pneumonitis and pulmonary oedema)
Gastrointestinal disorders		
	Common:	Decreased appetite, mild nausea and vomiting
	Rare:	Abdominal discomfort, constipation, diarrhoea
	Very rare:	Pancreatitis
Hepatobiliary disorders		
	Rare:	Intrahepatic cholestasis, jaundice
Skin and subcutaneous tissue disorders		
	Common:	Urticaria and other forms of rash
	Rare:	Photosensitivity reactions
	Very rare:	Cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, vasculitis necrotising and toxic epidermal necrolysis
	Not known:	Erythema multiforme
Musculoskeletal and connective tissue disorders		
	Not known:	Muscle spasm
Renal and urinary disorders		
	Not known:	Renal dysfunction, acute renal failure

Reproductive system and breast disorders		
	Common:	Impotence
General disorders and administration site conditions		
	Not known:	Asthenia, pyrexia
Investigations		
	Very common:	Increases in cholesterol and triglycerides
	Rare:	Glycosuria

4.9 Overdose

No information is available on the treatment of overdose with Sprimeo HCT. The most likely manifestation of overdose would be hypotension, related to the antihypertensive effect of aliskiren.

Overdose with hydrochlorothiazide is associated with electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration 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 cardiac arrhythmias associated with the concomitant use of digitalis glycosides or certain antiarrhythmic medicinal products. If symptomatic hypotension should occur, supportive treatment should be initiated.

In a study conducted in patients with end stage renal disease (ESRD) receiving haemodialysis, dialysis clearance of aliskiren was low (< 2% of oral clearance). Therefore dialysis is not adequate to treat aliskiren over-exposure.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Renin inhibitor (aliskiren) combinations with diuretics (hydrochlorothiazide), ATC code: C09XA52
Sprimeo HCT combines two antihypertensive compounds to control blood pressure in patients with essential hypertension: Aliskiren belongs to the class of direct renin inhibitors and hydrochlorothiazide to the class of thiazide diuretics. The combination of these substances with complementary mechanisms of action provides an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Aliskiren
Aliskiren is an orally active, non-peptide, potent and selective direct inhibitor of human renin.

By inhibiting the enzyme renin, aliskiren inhibits the RAAS at the point of activation, blocking the conversion of angiotensinogen to angiotensin I and decreasing levels of angiotensin I and angiotensin II. Whereas other agents that inhibit the RAAS (angiotensin converting enzyme inhibitors (ACEI) and angiotension II receptor blockers (ARB)) cause a compensatory rise in plasma renin activity (PRA), treatment with aliskiren decreases PRA in hypertensive patients by approximately 50 to 80%. Similar reductions were found when aliskiren was combined with other antihypertensive agents. The clinical implications of the effects on PRA are not known at the present time.

In hypertensive patients, once-daily administration of aliskiren at doses of 150 mg and 300 mg provided dose-dependent reductions in both systolic and diastolic blood pressure that were maintained over the entire 24-hour dose interval (maintaining benefit in the early morning) with a mean peak to trough ratio for diastolic response of up to 98% for the 300 mg dose. 85 to 90% of the maximal blood-pressure-lowering effect was observed after 2 weeks. The blood-pressure-lowering effect was sustained during long-term treatment (12 months), and was independent of age, gender, body mass index and ethnicity.

Combination therapy studies are available for aliskiren added to the diuretic hydrochlorothiazide, the calcium channel blocker amlodipine and the beta blocker atenolol. These combinations were efficacious and well tolerated.

The efficacy and safety of aliskiren-based therapy were compared to ramipril-based therapy in a 9-month non-inferiority study in 901 elderly patients (≥ 65 years) with essential systolic hypertension. Aliskiren 150 mg or 300 mg per day or ramipril 5 mg or 10 mg per day were administered for 36 weeks with optional add-on therapy of hydrochlorothiazide (12.5 mg or 25 mg) at week 12, and amlodipine (5 mg or 10 mg) at week 22. Over the 12 week period, aliskiren monotherapy lowered systolic/diastolic blood pressure by 14.0/5.1 mmHg, compared to 11.6/3.6 mmHg for ramipril, consistent with aliskiren being non-inferior to ramipril at the dosages chosen and the differences in systolic and diastolic blood pressure were statistically significant. Tolerability was comparable in both treatment arms, however cough was more often reported with the ramipril regimen than the aliskiren regimen (14.2% vs. 4.4%), whilst diarrhoea was more common with the aliskiren regimen than for the ramipril regimen (6.6% vs. 5.0%).

In a 8-week study in 754 hypertensive elderly (≥ 65 years) and very elderly patients (30% ≥ 75 years) aliskiren at doses of 75 mg, 150 mg and 300 mg provided statistically significant superior reduction in blood pressure (both systolic and diastolic) when compared to placebo. No additional blood pressure lowering effect was detected with 300 mg aliskiren compared to 150 mg aliskiren. All three doses were well tolerated in both elderly and very elderly patients.

There has been no evidence of first-dose hypotension and no effect on pulse rate in patients treated in controlled clinical studies. With cessation of treatment, blood pressure gradually returned towards baseline levels over a period of several weeks, with no evidence of a rebound effect for blood pressure or PRA.

In a 36-week study involving 820 patients with ischaemic left ventricular dysfunction, no changes in ventricular remodelling as assessed by left ventricular end systolic volume were detected with aliskiren compared to placebo on top of background therapy.

The combined rates of cardiovascular death, hospitalisation for heart failure, recurrent heart attack, stroke and resuscitated sudden death were similar in the aliskiren group and the placebo group. However, in patients receiving aliskiren there was a significantly higher rate of hyperkalaemia, hypotension and kidney dysfunction when compared to the placebo group.

Aliskiren was evaluated for cardiovascular and/or renal benefit in a double-blind placebo controlled randomised trial in 8,606 patients with type 2 diabetes and chronic kidney disease (evidenced by proteinuria and/or GFR < 60 ml/min/1.73 m^2) with or without cardiovascular disease. In most patients arterial blood pressure was well controlled at baseline. The primary endpoint was a composite of cardiovascular and renal complications.

In this study, aliskiren 300 mg was compared to placebo when added to standard of care which included either an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker. The study was discontinued prematurely because the participants were unlikely to benefit from aliskiren. Preliminary study results indicated a hazard ratio for the primary endpoint of 1.09 in favour of placebo (95% Confidence Interval: 0.97, 1.22, 2-sided p=0.17). In addition, an increased incidence of serious adverse outcomes was observed with aliskiren compared to placebo for renal complications (4.7% versus 3.3%), hyperkalaemia (36.9% versus 27.1%), hypotension (18.4% versus 14.6%) and stroke (2.7% versus 2.0%). The increased incidence of non-fatal stroke was greater in patients with renal insufficiency.

Hydrochlorothiazide
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 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.

Aliskiren/hydrochlorothiazide
Over 3,900 hypertensive patients received Sprimeo HCT once daily in clinical trials.

In hypertensive patients, once-daily administration of Sprimeo HCT provided dose-dependent reductions in both systolic and diastolic blood pressure that were maintained over the entire 24-hour dose interval. The antihypertensive effect is largely manifested within 1 week and the maximum effect is generally seen within 4 weeks.The blood-pressure-lowering effect was sustained during long-term treatment, and was independent of age, gender, body mass index and ethnicity. The antihypertensive effect of a single dose of the combination persisted for 24 hours. Upon withdrawal of the aliskiren treatment (aliskiren with or without hydrochlorothiazide add-on), the return of blood pressure towards baseline was gradual (3-4 weeks) with no evidence of the rebound effect.

Sprimeo HCT was studied in a placebo-controlled trial including 2,762 hypertensive patients with diastolic blood pressure ≥ 95 mmHg and < 110 mmHg (mean baseline blood pressure of 153.6/99.2 mmHg). In this study, Sprimeo HCT in doses from 150 mg/12.5 mg to 300 mg/25 mg produced dose-dependent blood pressure reductions (systolic/diastolic) from 17.6/11.9 mmHg to 21.2/14.3 mmHg, respectively, compared to 7.5/6.9 mmHg with placebo. The greater blood pressure reductions with these combination doses were also significantly greater than the respective doses of aliskiren and hydrochlorothiazide when used alone. The combination of aliskiren and hydrochlorothiazide neutralised the reactive increase of PRA caused by hydrochlorothiazide.

When administered in hypertensive patients with markedly elevated blood pressure (systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 100 mmHg), Sprimeo HCT in doses from 150 mg/12.5 mg to 300 mg/25 mg administered without up-titration from monotherapy demonstrated significantly greater systolic/diastolic blood pressure control rates (< 140/90 mmHg) as compared to the respective monotherapies. In this population, Sprimeo HCT 150 mg/12.5 mg to 300 mg/25 mg provided dose-dependent systolic/diastolic blood pressure reduction from 20.6/12.4 mmHg to 24.8/14.5 mmHg, which were significantly superior to the respective monotherapies. The safety of the combination therapy was similar to the respective monotherapies regardless of severity of hypertension or of the presence or absence of additional cardiovascular risk. Hypotension and related adverse events were uncommon with the combination treatment, with no increased incidence in elderly patients.

In a study in 880 randomised patients not adequately responsive to aliskiren 300 mg treatment, the combination of aliskiren/hydrochlorothiazide 300 mg/25 mg produced systolic/diastolic blood pressure reductions of 15.8/11.0 mmHg, which were significantly greater than aliskiren 300 mg monotherapy. In a study in 722 randomised patients not adequately responsive to hydrochlorothiazide 25 mg treatment, the combination of aliskiren/hydrochlorothiazide 300 mg/25 mg produced systolic/diastolic blood pressure reductions of 16.78/10.7 mmHg, which were significantly greater than hydrochlorothiazide 25 mg monotherapy.

In another clinical trial, the efficacy and safety of Sprimeo HCT were also assessed in 489 obese hypertensive patients who did not respond to hydrochlorothiazide 25 mg (baseline systolic/diastolic blood pressure 149.4/96.8 mmHg). In this difficult-to-treat population, Sprimeo HCT provided a blood pressure reduction (systolic/diastolic) of 15.8/11.9 mmHg compared to 15.4/11.3 mmHg for irbesartan/hydrochlorothiazide, 13.6/10.3 mmHg for amlodipine/hydrochlorothiazide and 8.6/7.9 mmHg for hydrochlorothiazide monotherapy, with similar safety to hydrochlorothiazide monotherapy.

In a study in 183 randomised patients with severe hypertension (mean sitting diastolic blood pressure ≥ 105 and < 120 mmHg), aliskiren treatment regimen with optional addition of hydrochlorothiazide 25 mg was shown to be safe and efficacious in reducing blood pressure.

5.2 Pharmacokinetic properties

Aliskiren

Absorption

Following oral absorption, peak plasma concentrations of aliskiren are reached after 1-3 hours. The absolute bioavailability of aliskiren is approximately 2-3%. Meals with a high fat content reduce C_{max} by 85% and AUC by 70%. Steady-state-plasma concentrations are reached within 5-7 days following once-daily administration and steady-state levels are approximately 2-fold greater than with the initial dose.

Distribution

Following intravenous administration, the mean volume of distribution at steady state is approximately 135 litres, indicating that aliskiren distributes extensively into the extravascular space. Aliskiren plasma protein binding is moderate (47-51%) and independent of the concentration.

Metabolism and elimination

The mean half-life is about 40 hours (range 34-41 hours). Aliskiren is mainly eliminated as unchanged compound in the faeces (oral radioactive dose recovery = 91%). Approximately 1.4% of the total oral dose is metabolised. The enzyme responsible for this metabolism is CYP3A4. Approximately 0.6% of the dose is recovered in urine following oral administration. Following intravenous administration, the mean plasma clearance is approximately 9 l/h.

Linearity

Exposure to aliskiren increased slightly more than in proportion to the increase in dose. After single dose administration in the dose range of 75 to 600 mg, a 2-fold increase in dose results in a ~2.3 and 2.6-fold increase in AUC and C_{max}, respectively. Mechanisms responsible for the deviation from dose proportionality have not been identified. A possible mechanism is saturation of transporters at the absorption site or at the hepatobiliary clearance route.

Hydrochlorothiazide

Absorption

The absorption of hydrochlorothiazide, after an oral dose, is rapid (T_{max} about 2 h). 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.

Metabolism and elimination
Hydrochlorothiazide is eliminated predominantly as unchanged compound. 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. There is more than 95% of the absorbed dose being excreted as unchanged compound in the urine. The renal clearance is composed of passive filtration and active secretion into the renal tubule.

Aliskiren/hydrochlorothiazide
Following oral administration of Sprimeo HCT tablets, the median peak plasma concentration time is within 1 hour for aliskiren and 2.5 hours for hydrochlorothiazide.

The rate and extent of absorption of Sprimeo HCT are equivalent to the bioavailability of aliskiren and hydrochlorothiazide when administered as individual monotherapies. Similar food effect was observed for Sprimeo HCT as for the individual monotherapies.

Characteristics in patients
Sprimeo HCT has been shown to be effective as a once-a-day antihypertensive treatment in adult patients, regardless of gender, age, body mass index and ethnicity.

The pharmacokinetics of aliskiren are not significantly affected in patients with mild to moderate liver disease. Consequently, no initial dose adjustment of Sprimeo HCT is required in patients with mild to moderate hepatic impairment. No data are available on patients with severe hepatic impairment treated by Sprimeo HCT. Sprimeo HCT is contraindicated in patients with severe hepatic impairment (see section 4.3).

No adjustment of the initial dose is required for patients with mild to moderate renal impairment (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. Sprimeo HCT is contraindicated in patients with anuria or severe renal impairment (GFR < 30 ml/min/1.73 m^2) and the concomitant use of Sprimeo HCT with ARBs or ACEIs is contraindicated in patients with renal impairment (GFR < 60 ml/min/1.73 m^2) (see section 4.3).

The pharmacokinetics of aliskiren were evaluated in patients with end stage renal disease receiving haemodialysis. Administration of a single oral dose of 300 mg aliskiren was associated with very minor changes in the pharmacokinetics of aliskiren (change in C_{max} of less than 1.2 fold; increase in AUC of up to 1.6 fold) compared to matched healthy subjects. Timing of haemodialysis did not significantly alter the pharmacokinetics of aliskiren in ESRD patients. Therefore, if administration of aliskiren in ESRD patients receiving haemodialysis is considered necessary, no dose adjustment is warranted in these patients. However, the use of aliskiren is not recommended in patients with severe renal impairment (see section 4.4).

No initial dose adjustment of Sprimeo HCT is required in elderly patients. Limited data suggest that the systemic clearance of hydrochlorothiazide is reduced in both healthy and hypertensive elderly subjects compared to young healthy volunteers.

No pharmacokinetic data are available in the paediatric population.

5.3 Preclinical safety data

Safety pharmacology studies with aliskiren did not reveal any adverse effects on central nervous, respiratory or cardiovascular function. Findings during repeat-dose toxicity studies in animals were consistent with the known local irritation potential or the expected pharmacological effects of aliskiren. No carcinogenic potential for aliskiren was detected in a 2-year rat study and a 6-month transgenic mouse study. One colonic adenoma and one caecal adenocarcinoma recorded in rats at the dose of 1,500 mg/kg/day were not statistically significant. Aliskiren was devoid of any mutagenic potential, embryo-foetal toxicity or teratogenicity. Fertility, prenatal development and postnatal development were unaffected in rats.

Preclinical evaluations to support the administration of hydrochlorothiazide in humans included *in vitro* genotoxicity assays and reproductive toxicity and carcinogenicity studies in rodents. Extensive clinical data are available for hydrochlorothiazide and these are reflected in the relevant sections.

The findings observed in the 2-week and 13-week toxicity studies were consistent with those observed previously with aliskiren or hydrochlorothiazide monotherapies. There were no new or unexpected findings observed of relevance to human use. Increased cellular vacuolation of the adrenal gland zona glomerulosa was observed during the 13-week toxicity study in rats. The finding was observed in animals treated with hydrochlorothiazide but not in those animals receiving aliskiren alone or vehicle. There was no evidence that this finding was enhanced in the aliskiren/hydrochlorothiazide combination as it was only apparent at a minimal severity in all animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Cellulose microcrystalline
Crospovidone
Lactose monohydrate
Wheat starch
Povidone
Magnesium stearate
Silica colloidal anhydrous
Talc

Coating:
Talc
Hypromellose
Macrogol
Titanium dioxide (E171)
Red iron oxide (E172)
Yellow iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

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

PA/Alu/PVC – Alu blisters:
Single-packs containing 7, 14, 28, 30, 50 or 56 tablets.
Multi-packs containing 90, 98 or 280 tablets.

PVC/polychlorotrifluoroethylene (PCTFE) – Alu blisters:
Single-packs containing 7, 14, 28, 30, 50, 56, 90 or 98 tablets.
Single-packs (perforated unit dose blister) containing 56 x 1 tablets.
Multi-packs containing 280 tablets.
Multi-packs (perforated unit dose blister) containing 98 x 1 tablets.

Not all pack sizes or strengths may be marketed.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/683/021-040

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23.06.2011

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Sprimeo HCT 300 mg/12.5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 300 mg aliskiren (as hemifumarate) and 12.5 mg hydrochlorothiazide.

Excipients: Each tablet contains 25 mg lactose monohydrate and 24.5 mg wheat starch.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Violet white, biconvex, ovaloid film-coated tablet imprinted with “CVI” on one side and “NVR” on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension in adults.

Sprimeo HCT is indicated in patients whose blood pressure is not adequately controlled on aliskiren or hydrochlorothiazide used alone.

Sprimeo HCT is indicated as substitution therapy in patients adequately controlled with aliskiren and hydrochlorothiazide, given concurrently, at the same dose level as in the combination.

4.2 Posology and method of administration

The recommended dose of Sprimeo HCT is one tablet per day. Sprimeo HCT should be taken with a light meal once a day, preferably at the same time each day. Grapefruit juice should not be taken together with Sprimeo HCT.

The antihypertensive effect is largely manifested within 1 week and the maximum effect is generally seen within 4 weeks.

<u>Posology in patients not adequately controlled with aliskiren or hydrochlorothiazide monotherapy</u>
Individual dose titration with each of the two components may be recommended before changing to the fixed combination. When clinically appropriate, direct change from monotherapy to the fixed combination may be considered.

Sprimeo HCT 300 mg /12.5 mg may be administered in patients whose blood pressure is not adequately controlled with aliskiren 300 mg or hydrochlorothiazide 12.5 mg alone or by Sprimeo HCT 150 mg/12.5 mg.

If blood pressure remains uncontrolled after 2-4 weeks of therapy, the dose may be titrated up to a maximum of Sprimeo HCT 300 mg/25 mg daily. Dosing should be individualised and adjusted according to the patient’s clinical response.

Posology as substitution therapy
For convenience, patients receiving aliskiren and hydrochlorothiazide from separate tablets may be switched to a fixed combination tablet of Sprimeo HCT containing the same component doses.

Renal impairment
No adjustment of the initial dose is required for patients with mild to moderate renal impairment (see sections 4.4 and 5.2). Due to the hydrochlorothiazide component, Sprimeo HCT is contraindicated for use in patients with anuria and in patients with severe renal impairment (glomerular filtration rate (GFR) < 30 ml/min/1.73 m^2). The concomitant use of Sprimeo HCT with angiotensin II receptor blockers (ARB) or angiotensin converting enzyme inhibitors (ACEI) is contraindicated in patients with renal impairment (GFR < 60 ml/min/1.73 m^2) (see sections 4.3, 4.4 and 5.2).

Hepatic impairment
No adjustment of the initial dose is required for patients with mild to moderate hepatic impairment (see section 5.2). Sprimeo HCT is contraindicated in patients with severe hepatic impairment (see sections 4.3 and 4.4).

Elderly patients (over 65 years)
The recommended starting dose of aliskiren in elderly patients is 150 mg. No clinically meaningful additional blood pressure reduction is observed by increasing the dose to 300 mg in the majority of elderly patients.

Paediatric patients
Sprimeo HCT is not recommended for use in children and adolescents below age 18 due to a lack of data on safety and efficacy (see section 5.2).

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients (see section 6.1), or to other sulphonamide-derived substances.
- History of angioedema with aliskiren.
- Hereditary or idiopathic angioedema.
- Second and third trimesters of pregnancy (see section 4.6).
- Anuria.
- Severe renal impairment (GFR < 30 ml/min/1.73 m^2).
- Refractory hypokalaemia, hyponatraemia, hypercalcaemia and symptomatic hyperuricaemia.
- Severe hepatic impairment.
- The concomitant use of aliskiren with ciclosporin and itraconazole, two highly potent P-glycoprotein (P-gp) inhibitors, and other potent P-gp inhibitors (e.g. quinidine), is contraindicated (see section 4.5).
- The concomitant use of aliskiren with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) (see sections 4.2, 4.4, 4.5 and 5.1).

4.4 Special warnings and precautions for use

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
Hypotension, syncope, stroke, hyperkalaemia, and changes in renal function (including acute renal failure) have been reported in susceptible individuals, especially if combining medicinal products that affect this system (see section 5.1). Dual blockade of the renin-angiotensin-aldosterone system by combining aliskiren with an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin II receptor blocker (ARB) is therefore not recommended.

The use of aliskiren in combination with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) (see section 4.3).

Heart failure
Aliskiren should be used with caution in patients with serious congestive heart failure (New York Heart Association (NYHA) functional class III-IV). Sprimeo HCT should be used with caution in patients with heart failure due to limited clinical efficacy and safety data.

Angioedema
As with other agents acting on the renin-angiotensin system, angioedema or symptoms suggestive of angioedema (swelling of the face, lips, throat and/or tongue) have been reported in patients treated with aliskiren.

A number of these patients had a history of angioedema or symptoms suggestive of angioedema, which in some cases followed use of other medicines that can cause angioedema, including RAAS blockers (angiotensin converting enzyme inhibitors or angiotensin receptor blockers) (see section 4.8).

Patients with a history of angioedema may be at increased risk of experiencing angioedema during treatment with aliskiren (see sections 4.3 and 4.8). Caution should therefore be exercised when prescribing aliskiren to patients with a history of angioedema, and such patients should be closely monitored during treatment (see section 4.8) especially at the beginning of the treatment.

If angioedema occurs, Sprimeo HCT should be promptly discontinued and appropriate therapy and monitoring provided until complete and sustained resolution of signs and symptoms has occurred. Where there is involvement of the tongue, glottis or larynx adrenaline should be administered. In addition, measures necessary to maintain patent airways should be provided.

Sodium- and/or volume-depleted patients
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 Sprimeo HCT. Sprimeo HCT should be used only after correction of any pre-existing sodium and/or volume depletion.

Electrolyte imbalance
Treatment with Sprimeo 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 Sprimeo HCT should be discontinued until stable correction of the potassium balance. Although hypokalaemia may develop with the use of thiazide diuretics, concurrent therapy with aliskiren may reduce diuretic-induced hypokalaemia. The risk of hypokalaemia is greater in patients with cirrhosis of the liver, patients experiencing brisk diuresis, patients with inadequate oral electrolyte intake and patients receiving concomitant therapy with corticosteroids or adrenocorticotropic hormone (ACTH) (see sections 4.5 and 4.8).

Conversely, increases in serum potassium have been observed with aliskiren in post-marketing experience and these may be exacerbated by concomitant use of other agents acting on the RAAS or by non-steroidal anti-inflammatory drugs (NSAIDs). Consistent with standard medical practice, periodic determination of renal function including serum electrolytes is advised if co-administration is considered necessary. The concomitant use of aliskiren and ACEIs or ARBs is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) (see sections 4.3, 4.5 and 4.8).

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 Sprimeo HCT therapy, the treatment should be discontinued until normalisation of natraemia.

There is no evidence that Sprimeo HCT would reduce or prevent diuretic-induced hyponatraemia. Chloride deficit is generally mild and usually does not require treatment.

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

Thiazides reduce urinary calcium excretion and may cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Sprimeo HCT is contraindicated in patients with hypercalcaemia and should only be used after correction of any pre-existing hypercalcaemia. Sprimeo 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.

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

No dosage adjustment is necessary in patients with mild to moderate renal impairment (GFR $\geq$ 30 ml/min/1.73 m^2).

There is no experience regarding the administration of Sprimeo HCT in patients who have recently undergone kidney transplantation.

As for other agents acting on the renin-angiotensin system, caution should be exercised when aliskiren is given in the presence of conditions pre-disposing to kidney dysfunction such as hypovolaemia (e.g. due to blood loss, severe or prolonged diarrhoea, prolonged vomiting, etc.), heart disease, liver disease, diabetes mellitus or kidney disease. The concomitant use of aliskiren and ACEIs or ARBs is contraindicated in patients with renal impairment (GFR < 60 ml/min/1.73 m^2). Acute renal failure, reversible upon discontinuation of treatment, has been reported in at-risk patients receiving aliskiren in post-marketing experience. In the event that any signs of renal failure occur, aliskiren should be promptly discontinued.

Hepatic impairment
Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. No adjustment of the initial dose is required for patients with mild to moderate hepatic impairment. No data are available for the use of Sprimeo HCT in patients with severe hepatic impairment. Due to the hydrochlorothiazide component, Sprimeo HCT is contraindicated in patients with severe hepatic impairment (see sections 4.3 and 5.2).

There is no clinical experience with Sprimeo HCT in patients with hepatic impairment.

Moderate P-gp inhibitors
Co-administration of aliskiren 300 mg with ketoconazole 200 mg or verapamil 240 mg resulted in a 76% or 97% increase in aliskiren AUC, respectively. Therefore caution should be exercised when aliskiren is administered with moderate P-gp inhibitors such as ketoconazole or verapamil (see section 4.5).

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy
As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Renal artery stenosis and renovascular hypertension
No controlled clinical data are available on the use of Sprimeo HCT in patients with unilateral or bilateral renal artery stenosis, or stenosis to a solitary kidney. However, as with other agents acting on the renin-angiotensin system, there is an increased risk of renal insufficiency, including acute renal failure, when patients with renal artery stenosis are treated with aliskiren. Therefore caution should be exercised in these patients. If renal failure occurs, treatment should be discontinued.

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

Metabolic and endocrine effects
Thiazide diuretics, including hydrochlorothiazide, may alter glucose tolerance and raise serum levels of cholesterol and triglycerides, and uric acid. In diabetic patients dosage adjustments of insulin or oral hypoglycaemic agents may be required. Concomitant use of Sprimeo HCT with ARBs or ACEIs is contraindicated in patients with diabetes mellitus (see section 4.3).

Due to the hydrochlorothiazide component, Sprimeo HCT is contraindicated in symptomatic hyperuricaemia (see section 4.3). 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 an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Sprimeo HCT is contraindicated in patients with hypercalcaemia and should only be used after correction of any pre-existing hypercalcaemia. Sprimeo 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 Sprimeo HCT, it is recommended to stop the treatment. If a re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Acute angle-closure glaucoma
Hydrochlorothiazide, a sulphonamide, has been associated with an idiosyncratic reaction resulting in 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 weeks 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
In the event of severe and persistent diarrhoea, Sprimeo HCT therapy should be stopped.

As with any antihypertensive agent, excessive reduction of blood pressure in patients with ischaemic cardiopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke.

Hypersensitivity reactions to hydrochlorothiazide may occur in patients, but are more likely in patients with allergy and asthma.

Excipients
Sprimeo HCT contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sprimeo HCT contains wheat starch. It is suitable for people with coeliac disease. Patients with wheat allergy (different from coeliac disease) should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Information on Sprimeo HCT interactions
Medicinal products affecting serum potassium levels: The potassium-depleting effect of hydrochlorothiazide is attenuated by the potassium-sparing effect of aliskiren. However, this effect of hydrochlorothiazide on serum potassium would be expected to be potentiated by other medicinal products associated with potassium loss and hypokalaemia (e.g. other kaliuretic diuretics, corticosteroids, laxatives, adrenocorticotropic hormone (ACTH), amphotericin, carbenoxolone, penicillin G, salicylic acid derivatives). Conversely, concomitant use of other agents affecting the RAAS, of NSAIDs or of agents that increase serum potassium levels (e.g. potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, heparin) may lead to increases in serum potassium. If co-medication with an agent affecting the level of serum potassium is considered necessary, caution is advisable. The combination of aliskiren with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) and is not recommended in other patients (see sections 4.3, 4.4 and 5.1).

Medicinal products affected by serum potassium disturbances: Periodic monitoring of serum potassium is recommended when Sprimeo HCT is administered with medicinal products affected by serum potassium disturbances (e.g. digitalis glycosides, antiarrhythmics).

Non-steroidal anti-inflammatory drugs (NSAIDs), including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors), acetylsalicylic acid and non-selective NSAIDs: As with other agents acting on the renin-angiotensin system, NSAIDs may reduce the anti-hypertensive effect of aliskiren. NSAIDs may also weaken the diuretic and antihypertensive activity of hydrochlorothiazide.

In some patients with compromised renal function (dehydrated patients or elderly patients) aliskiren and hydrochlorothiazide given concomitantly with NSAIDs may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore the use of Sprimeo HCT with an NSAID requires caution, especially in elderly patients.

Other antihypertensive agents: The antihypertensive effect of Sprimeo HCT may be increased with the concomitant use of other antihypertensive agents.

Additional information on aliskiren interactions
The combination of aliskiren with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) and is not recommended in other patients (see sections 4.3, 4.4 and 5.1).

Compounds that have been investigated in aliskiren clinical pharmacokinetic studies include acenocoumarol, atenolol, celecoxib, fenofibrate, pioglitazone, allopurinol, isosorbide-5-mononitrate, digoxin, metformin, amlodipine, atorvastatin, cimetidine and hydrochlorothiazide. No clinically relevant interactions have been identified. As a result no dose adjustment for aliskiren or these co-administered medicinal products is necessary.

P-glycoprotein interactions: MDR1/Mdr1a/1b (P-gp) was found to be the major efflux system involved in intestinal absorption and biliary excretion of aliskiren in preclinical studies. Rifampicin, which is an inducer of P-gp, reduced aliskiren bioavailability by approximately 50% in a clinical study. Other inducers of P-gp (St. John's wort) might decrease the bioavailability of aliskiren. Although this has not been investigated for aliskiren, it is known that P-gp also controls tissue uptake of a variety of substrates and P-gp inhibitors can increase the tissue-to-plasma concentration ratios. Therefore, P-gp inhibitors may increase tissue levels more than plasma levels. The potential for drug interactions at the P-gp site will likely depend on the degree of inhibition of this transporter.

P-gp potent inhibitors: A single dose drug interaction study in healthy subjects has shown that ciclosporin (200 and 600 mg) increases C_{max} of aliskiren 75 mg approximately 2.5-fold and AUC approximately 5-fold. The increase may be higher with higher aliskiren doses. In healthy subjects, itraconazole (100 mg) increases AUC and C_{max} of aliskiren (150 mg) by 6.5-fold and 5.8-fold, respectively. Therefore, concomitant use of aliskiren and P-gp potent inhibitors is contraindicated (see section 4.3).

Moderate P-gp inhibitors: Co-administration of ketoconazole (200 mg) or verapamil (240 mg) with aliskiren (300 mg) resulted in a 76% or 97% increase in aliskiren AUC, respectively. The change in plasma levels of aliskiren in the presence of ketoconazole or verapamil is expected to be within the range that would be achieved if the dose of aliskiren were doubled; aliskiren doses of up to 600 mg, or twice the highest recommended therapeutic dose, have been found to be well tolerated in controlled clinical trials. Preclinical studies indicate that aliskiren and ketoconazole co-administration enhances aliskiren gastrointestinal absorption and decreases biliary excretion. Therefore, caution should be exercised when aliskiren is administered with ketoconazole, verapamil or other moderate P-gp inhibitors (clarithromycin, telithromycin, erythromycin, amiodarone).

P-gp substrates or weak inhibitors: No relevant interactions with atenolol, digoxin, amlodipine or cimetidine have been observed. When administered with atorvastatin (80 mg), steady-state aliskiren (300 mg) AUC and C_{max} increased by 50%.

Organic anion transporting polypeptide (OATP) inhibitors: Preclinical studies indicate that aliskiren might be a substrate of organic anion transporting polypeptides. Therefore, the potential exists for interactions between OATP inhibitors and aliskiren when administered concomitantly (see interaction with Grapefruit juice).

Grapefruit juice: Administration of grapefruit juice with aliskiren resulted in a decrease in AUC and C_{max} of aliskiren. Co-administration with aliskiren 150 mg resulted in a 61% decrease in aliskiren AUC and co-administration with aliskiren 300 mg resulted in a 38% decrease in aliskiren AUC. This decrease is likely due to an inhibition of organic anion transporting polypeptide-mediated uptake of aliskiren by grapefruit juice in the gastrointestinal tract. Therefore, because of the risk of therapeutic failure, grapefruit juice should not be taken together with Sprimeo HCT.

Furosemide: When aliskiren was co-administered with furosemide, the AUC and C_{max} of furosemide were reduced by 28% and 49%, respectively. It is therefore recommended to monitor the effects when initiating and adjusting furosemide therapy to avoid possible underutilisation in clinical situations of volume overload.

Warfarin: The effects of aliskiren on warfarin pharmacokinetics have not been evaluated.

Food interactions: Meals with a high fat content have been shown to reduce the absorption of aliskiren substantially.

Additional information on hydrochlorothiazide interactions
When administered concurrently, the following medicinal products may interact with thiazide diuretics:

Lithium: Renal clearance of lithium is reduced by thiazides, therefore the risk of lithium toxicity may be increased with hydrochlorothiazide. Co-administration of lithium and hydrochlorothiazide is not recommended. If this combination proves essential, careful monitoring of serum lithium level is recommended during concomitant use.

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 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.

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.

Digoxine or other digitalis glycosides: Thiazide-induced hypokalaemia or hypomagnesaemia may occur as undesirable effects, favouring the onset of digitalis-induced cardiac arrhythmias.

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.

Antidiabetic agents (e.g. insulin and oral antidiabetic agents): Thiazides may alter glucose tolerance. Dose adjustment of the antidiabetic medicinal product may be necessary (see section 4.4). 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.

Medicinal products used in the treatment of gout: 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.

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.

Amantadine: Thiazides, including hydrochlorothiazide, may increase the risk of adverse reactions caused by amantadine.

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.

Cytotoxic agents: Thiazides, including hydrochlorothiazide, may reduce the renal excretion of cytotoxic agents (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.

Non-depolarising skeletal muscle relaxants: Thiazides, including hydrochlorothiazide, potentiate the action of skeletal muscle relaxants such as curare derivatives.

Alcohol, barbiturates or narcotics: Concomitant administration of thiazide diuretics with subtances that also have a blood pressure lowering effect (e.g. by reducing sympathetic central nervous system activity or direct vasodilatation) may potentiate orthostatic hypotension.

Methyldopa: There have been isolated reports of haemolytic anaemia occurring with concomitant use of hydrochlorothiazide and methyldopa.

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 rehydrated before administration.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data on the use of aliskiren in pregnant women. Aliskiren was not teratogenic in rats or rabbits (see section 5.3). Other substances that act directly on the RAAS have been associated with serious foetal malformations and neonatal death when used during second and third trimesters. 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.

Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or pre-eclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.

Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

No specific clinical studies have been performed with this combination, therefore Sprimeo HCT should not be used during the first trimester of pregnancy or in women planning to become pregnant and is contraindicated during the second and third trimesters (see section 4.3). A switch to a suitable alternative treatment should be carried out in advance of a planned pregnancy. If pregnancy is detected during therapy, Sprimeo HCT should be discontinued as soon as possible.

Breast-feeding
It is not known whether aliskiren is excreted in human milk. Aliskiren was secreted in the milk of lactating rats.

Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit milk production.

The use of Sprimeo HCT during breast-feeding is not recommended. If Sprimeo HCT is used during breast-feeding, doses should be kept as low as possible.

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed. Sprimeo HCT is unlikely to affect the ability to drive and use machines. However, when driving vehicles or operating machinery it must be borne in mind that dizziness or drowsiness may occasionally occur when taking antihypertensive therapy.

4.8 Undesirable effects

Aliskiren/hydrochlorothiazide combination
The safety of Sprimeo HCT has been evaluated in 9 clinical trials with more than 3,900 patients, including over 700 treated for over 6 months, and 190 for over 1 year. The incidence of adverse reactions showed no association with gender, age, body mass index, race or ethnicity. Treatment with Sprimeo HCT had an overall incidence of adverse experiences at doses up to 300 mg/25 mg similar to placebo. Adverse reactions have generally been mild and transient in nature and have only infrequently required discontinuation of therapy. The most common adverse drug reaction observed with Sprimeo HCT is diarrhoea. The adverse drug reactions previously reported with one of the individual components of Sprimeo HCT (aliskiren and hydrochlorothiazide) and listed in the respective paragraphs on the individual components may occur with Sprimeo HCT.

The frequency of adverse reactions listed below is defined using the following convention: 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) and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Gastrointestinal disorders	
Common:	Diarrhoea

Diarrhoea: Diarrhoea is a dose-related adverse drug reaction for aliskiren. In controlled clinical trials, the incidence of diarrhoea in Sprimeo HCT-treated patients was 1.3% compared to 1.4% for aliskiren- or 1.9% for hydrochlorothiazide-treated patients.

Serum potassium: In a large placebo-controlled clinical trial, the opposite effects of aliskiren (150 mg or 300 mg) and hydrochlorothiazide (12.5 mg or 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 potassium to detect possible electrolyte imbalance should be performed in patients at risk at appropriate intervals (see sections 4.4 and 4.5).

Additional information on individual components
Other adverse reactions previously reported with one of the individual components may occur with Sprimeo HCT even if not observed in clinical trials.

Aliskiren
Treatment with Aliskiren up to 300 mg resulted in an overall incidence of adverse reactions similar to placebo. Adverse reactions have generally been mild and transient in nature and have only infrequently required discontinuation of therapy. The most common adverse drug reaction is diarrhoea.

The known aliskiren adverse drug reactions are presented in the table below using the same convention as described previously for the fixed combination.

Nervous system disorders		
	Common:	Dizziness
Vascular disorders		
	Uncommon:	Hypotension
Gastrointestinal disorders		
	Common:	Diarrhoea
Immune system disorders		
	Rare:	Hypersensitivity reactions
Skin and subcutaneous tissue disorders		
	Uncommon:	Rash, severe cutaneous adverse reactions (SCARs) including toxic epidermal necrolysis (TEN) and oral mucosal reactions
	Rare:	Angioedema
Musculoskeletal and connective tissue disorders		
	Common:	Arthralgia
Renal and urinary disorders		
	Uncommon:	Acute renal failure, renal impairment
General disorders and administration site conditions		
	Uncommon:	Oedema peripheral
Investigations		
	Common:	Hyperkalaemia
	Rare:	Haemoglobin decreased, haematocrit decreased
	Rare:	Blood creatinine increased

Angioedema and hypersensitivity reactions have occurred during treatment with aliskiren. In controlled clinical trials, angioedema and hypersensitivity reactions occurred rarely during treatment with aliskiren with rates comparable to treatment with placebo or comparators.

Cases of angioedema or symptoms suggestive of angioedema (swelling of the face, lips, throat and/or tongue) have also been reported in post-marketing experience. A number of these patients had a history of angioedema or symptoms suggestive of angioedema which in some cases was associated with the administration of other medicines known to cause angioedema, including RAAS blockers (ACE inhibitors or ARBs).

Hypersensitivity reactions have also been reported in post-marketing experience.

In the event of any signs suggesting a hypersensitivity reaction/angioedema (in particular difficulties in breathing or swallowing, rash, itching, hives or swelling of the face, extremities, eyes, lips and/or tongue, dizziness) patients should discontinue treatment and contact the physician (see section 4.4).

Arthralgia has been reported in post-marketing experience. In some cases this occurred as part of a hypersensitivity reaction.

Haemoglobin and haematocrit: Small decreases in haemoglobin and haematocrit (mean decreases of approximately 0.05 mmol/l and 0.16 volume percent, respectively) were observed. No patients discontinued therapy due to anaemia. This effect is also seen with other agents acting on the renin-angiotensin system, such as ACEI and ARBs.

Serum potassium: Increases in serum potassium have been observed with aliskiren and these may be exacerbated by concomitant use of other agents acting on the RAAS or by NSAIDs. Consistent with standard medical practice, periodic determination of renal function including serum electrolytes is advised if co-administration is considered necessary. The combination of aliskiren with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) and is not recommended in other patients (see sections 4.3, 4.4 and 5.1).

In post-marketing experience, renal dysfunction and cases of acute renal failure have been reported in patients at risk (see section 4.4). There have also been reports of peripheral oedema, increase in blood creatinine and severe cutaneous adverse reactions (SCARs) including toxic epidermal necrolysis (TEN) and oral mucosal reactions.

Hydrochlorothiazide
Hydrochlorothiazide has been extensively prescribed for many years, frequently in higher doses than those contained in Sprimeo HCT. The following adverse reactions have been reported in patients treated with thiazide diuretics alone, including hydrochlorothiazide:

Blood and lymphatic system disorders		
	Rare:	Thrombocytopenia sometimes with purpura
	Very rare:	Agranulocytosis, bone marrow depression, haemolytic anaemia, leucopenia
	Not known:	Aplastic anaemia
Immune system disorders		
	Very rare:	Hypersensitivity
Metabolism and nutrition disorders		
	Very common:	Hypokalaemia
	Common:	Hyperuricaemia, hypomagnesaemia, hyponatraemia
	Rare:	Hypercalcaemia, hyperglycaemia, worsening of diabetic metabolic state
	Very rare:	Hypochloraemic alkalosis
Psychiatric disorders		
	Rare:	Depression, sleep disturbances
Nervous system disorders		
	Rare:	Dizziness, headache, paraesthesia
Eye disorders		
	Rare:	Visual impairment
	Not known:	Acute angle-closure glaucoma
Cardiac disorders		
	Rare:	Cardiac arrhythmias
Vascular disorders		
	Common:	Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders		
	Very rare:	Respiratory distress (including pneumonitis and pulmonary oedema)
Gastrointestinal disorders		
	Common:	Decreased appetite, mild nausea and vomiting
	Rare:	Abdominal discomfort, constipation, diarrhoea
	Very rare:	Pancreatitis
Hepatobiliary disorders		
	Rare:	Intrahepatic cholestasis, jaundice
Skin and subcutaneous tissue disorders		
	Common:	Urticaria and other forms of rash
	Rare:	Photosensitivity reactions
	Very rare:	Cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, vasculitis necrotising and toxic epidermal necrolysis
	Not known:	Erythema multiforme
Musculoskeletal and connective tissue disorders		
	Not known:	Muscle spasm
Renal and urinary disorders		
	Not known:	Renal dysfunction, acute renal failure

Reproductive system and breast disorders		
	Common:	Impotence
General disorders and administration site conditions		
	Not known:	Asthenia, pyrexia
Investigations		
	Very common:	Increases in cholesterol and triglycerides
	Rare:	Glycosuria

4.9 Overdose

No information is available on the treatment of overdose with Sprimeo HCT. The most likely manifestation of overdose would be hypotension, related to the antihypertensive effect of aliskiren.

Overdose with hydrochlorothiazide is associated with electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration 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 cardiac arrhythmias associated with the concomitant use of digitalis glycosides or certain antiarrhythmic medicinal products. If symptomatic hypotension should occur, supportive treatment should be initiated.

In a study conducted in patients with end stage renal disease (ESRD) receiving haemodialysis, dialysis clearance of aliskiren was low (< 2% of oral clearance). Therefore dialysis is not adequate to treat aliskiren over-exposure.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Renin inhibitor (aliskiren) combinations with diuretics (hydrochlorothiazide), ATC code: C09XA52
Sprimeo HCT combines two antihypertensive compounds to control blood pressure in patients with essential hypertension: Aliskiren belongs to the class of direct renin inhibitors and hydrochlorothiazide to the class of thiazide diuretics. The combination of these substances with complementary mechanisms of action provides an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Aliskiren
Aliskiren is an orally active, non-peptide, potent and selective direct inhibitor of human renin.

By inhibiting the enzyme renin, aliskiren inhibits the RAAS at the point of activation, blocking the conversion of angiotensinogen to angiotensin I and decreasing levels of angiotensin I and angiotensin II. Whereas other agents that inhibit the RAAS (angiotensin converting enzyme inhibitors (ACEI) and angiotension II receptor blockers (ARB)) cause a compensatory rise in plasma renin activity (PRA), treatment with aliskiren decreases PRA in hypertensive patients by approximately 50 to 80%. Similar reductions were found when aliskiren was combined with other antihypertensive agents. The clinical implications of the effects on PRA are not known at the present time.

In hypertensive patients, once-daily administration of aliskiren at doses of 150 mg and 300 mg provided dose-dependent reductions in both systolic and diastolic blood pressure that were maintained over the entire 24-hour dose interval (maintaining benefit in the early morning) with a mean peak to trough ratio for diastolic response of up to 98% for the 300 mg dose. 85 to 90% of the maximal blood-pressure-lowering effect was observed after 2 weeks. The blood-pressure-lowering effect was sustained during long-term treatment (12 months), and was independent of age, gender, body mass index and ethnicity.

Combination therapy studies are available for aliskiren added to the diuretic hydrochlorothiazide, the calcium channel blocker amlodipine and the beta blocker atenolol. These combinations were efficacious and well tolerated.

The efficacy and safety of aliskiren-based therapy were compared to ramipril-based therapy in a 9-month non-inferiority study in 901 elderly patients (≥ 65 years) with essential systolic hypertension. Aliskiren 150 mg or 300 mg per day or ramipril 5 mg or 10 mg per day were administered for 36 weeks with optional add-on therapy of hydrochlorothiazide (12.5 mg or 25 mg) at week 12, and amlodipine (5 mg or 10 mg) at week 22. Over the 12 week period, aliskiren monotherapy lowered systolic/diastolic blood pressure by 14.0/5.1 mmHg, compared to 11.6/3.6 mmHg for ramipril, consistent with aliskiren being non-inferior to ramipril at the dosages chosen and the differences in systolic and diastolic blood pressure were statistically significant. Tolerability was comparable in both treatment arms, however cough was more often reported with the ramipril regimen than the aliskiren regimen (14.2% vs. 4.4%), whilst diarrhoea was more common with the aliskiren regimen than for the ramipril regimen (6.6% vs. 5.0%).

In a 8-week study in 754 hypertensive elderly (≥ 65 years) and very elderly patients (30% ≥ 75 years) aliskiren at doses of 75 mg, 150 mg and 300 mg provided statistically significant superior reduction in blood pressure (both systolic and diastolic) when compared to placebo. No additional blood pressure lowering effect was detected with 300 mg aliskiren compared to 150 mg aliskiren. All three doses were well tolerated in both elderly and very elderly patients.

There has been no evidence of first-dose hypotension and no effect on pulse rate in patients treated in controlled clinical studies. With cessation of treatment, blood pressure gradually returned towards baseline levels over a period of several weeks, with no evidence of a rebound effect for blood pressure or PRA.

In a 36-week study involving 820 patients with ischaemic left ventricular dysfunction, no changes in ventricular remodelling as assessed by left ventricular end systolic volume were detected with aliskiren compared to placebo on top of background therapy.

The combined rates of cardiovascular death, hospitalisation for heart failure, recurrent heart attack, stroke and resuscitated sudden death were similar in the aliskiren group and the placebo group. However, in patients receiving aliskiren there was a significantly higher rate of hyperkalaemia, hypotension and kidney dysfunction when compared to the placebo group.

Aliskiren was evaluated for cardiovascular and/or renal benefit in a double-blind placebo controlled randomised trial in 8,606 patients with type 2 diabetes and chronic kidney disease (evidenced by proteinuria and/or GFR < 60 ml/min/1.73 m^2) with or without cardiovascular disease. In most patients arterial blood pressure was well controlled at baseline. The primary endpoint was a composite of cardiovascular and renal complications.

In this study, aliskiren 300 mg was compared to placebo when added to standard of care which included either an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker. The study was discontinued prematurely because the participants were unlikely to benefit from aliskiren. Preliminary study results indicated a hazard ratio for the primary endpoint of 1.09 in favour of placebo (95% Confidence Interval: 0.97, 1.22, 2-sided p=0.17). In addition, an increased incidence of serious adverse outcomes was observed with aliskiren compared to placebo for renal complications (4.7% versus 3.3%), hyperkalaemia (36.9% versus 27.1%), hypotension (18.4% versus 14.6%) and stroke (2.7% versus 2.0%). The increased incidence of non-fatal stroke was greater in patients with renal insufficiency.

Hydrochlorothiazide
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 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.

Aliskiren/hydrochlorothiazide
Over 3,900 hypertensive patients received Sprimeo HCT once daily in clinical trials.

In hypertensive patients, once-daily administration of Sprimeo HCT provided dose-dependent reductions in both systolic and diastolic blood pressure that were maintained over the entire 24-hour dose interval. The antihypertensive effect is largely manifested within 1 week and the maximum effect is generally seen within 4 weeks.The blood-pressure-lowering effect was sustained during long-term treatment, and was independent of age, gender, body mass index and ethnicity. The antihypertensive effect of a single dose of the combination persisted for 24 hours. Upon withdrawal of the aliskiren treatment (aliskiren with or without hydrochlorothiazide add-on), the return of blood pressure towards baseline was gradual (3-4 weeks) with no evidence of the rebound effect.

Sprimeo HCT was studied in a placebo-controlled trial including 2,762 hypertensive patients with diastolic blood pressure ≥ 95 mmHg and < 110 mmHg (mean baseline blood pressure of 153.6/99.2 mmHg). In this study, Sprimeo HCT in doses from 150 mg/12.5 mg to 300 mg/25 mg produced dose-dependent blood pressure reductions (systolic/diastolic) from 17.6/11.9 mmHg to 21.2/14.3 mmHg, respectively, compared to 7.5/6.9 mmHg with placebo. The greater blood pressure reductions with these combination doses were also significantly greater than the respective doses of aliskiren and hydrochlorothiazide when used alone. The combination of aliskiren and hydrochlorothiazide neutralised the reactive increase of PRA caused by hydrochlorothiazide.

When administered in hypertensive patients with markedly elevated blood pressure (systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 100 mmHg), Sprimeo HCT in doses from 150 mg/12.5 mg to 300 mg/25 mg administered without up-titration from monotherapy demonstrated significantly greater systolic/diastolic blood pressure control rates (< 140/90 mmHg) as compared to the respective monotherapies. In this population, Sprimeo HCT 150 mg/12.5 mg to 300 mg/25 mg provided dose-dependent systolic/diastolic blood pressure reduction from 20.6/12.4 mmHg to 24.8/14.5 mmHg, which were significantly superior to the respective monotherapies. The safety of the combination therapy was similar to the respective monotherapies regardless of severity of hypertension or of the presence or absence of additional cardiovascular risk. Hypotension and related adverse events were uncommon with the combination treatment, with no increased incidence in elderly patients.

In a study in 880 randomised patients not adequately responsive to aliskiren 300 mg treatment, the combination of aliskiren/hydrochlorothiazide 300 mg/25 mg produced systolic/diastolic blood pressure reductions of 15.8/11.0 mmHg, which were significantly greater than aliskiren 300 mg monotherapy. In a study in 722 randomised patients not adequately responsive to hydrochlorothiazide 25 mg treatment, the combination of aliskiren/hydrochlorothiazide 300 mg/25 mg produced systolic/diastolic blood pressure reductions of 16.78/10.7 mmHg, which were significantly greater than hydrochlorothiazide 25 mg monotherapy.

In another clinical trial, the efficacy and safety of Sprimeo HCT were also assessed in 489 obese hypertensive patients who did not respond to hydrochlorothiazide 25 mg (baseline systolic/diastolic blood pressure 149.4/96.8 mmHg). In this difficult-to-treat population, Sprimeo HCT provided a blood pressure reduction (systolic/diastolic) of 15.8/11.9 mmHg compared to 15.4/11.3 mmHg for irbesartan/hydrochlorothiazide, 13.6/10.3 mmHg for amlodipine/hydrochlorothiazide and 8.6/7.9 mmHg for hydrochlorothiazide monotherapy, with similar safety to hydrochlorothiazide monotherapy.

In a study in 183 randomised patients with severe hypertension (mean sitting diastolic blood pressure ≥ 105 and < 120 mmHg), aliskiren treatment regimen with optional addition of hydrochlorothiazide 25 mg was shown to be safe and efficacious in reducing blood pressure.

5.2 Pharmacokinetic properties

Aliskiren

Absorption

Following oral absorption, peak plasma concentrations of aliskiren are reached after 1-3 hours. The absolute bioavailability of aliskiren is approximately 2-3%. Meals with a high fat content reduce C_{max} by 85% and AUC by 70%. Steady-state-plasma concentrations are reached within 5-7 days following once-daily administration and steady-state levels are approximately 2-fold greater than with the initial dose.

Distribution

Following intravenous administration, the mean volume of distribution at steady state is approximately 135 litres, indicating that aliskiren distributes extensively into the extravascular space. Aliskiren plasma protein binding is moderate (47-51%) and independent of the concentration.

Metabolism and elimination

The mean half-life is about 40 hours (range 34-41 hours). Aliskiren is mainly eliminated as unchanged compound in the faeces (oral radioactive dose recovery = 91%). Approximately 1.4% of the total oral dose is metabolised. The enzyme responsible for this metabolism is CYP3A4. Approximately 0.6% of the dose is recovered in urine following oral administration. Following intravenous administration, the mean plasma clearance is approximately 9 l/h.

Linearity

Exposure to aliskiren increased slightly more than in proportion to the increase in dose. After single dose administration in the dose range of 75 to 600 mg, a 2-fold increase in dose results in a ~2.3 and 2.6-fold increase in AUC and C_{max}, respectively. Mechanisms responsible for the deviation from dose proportionality have not been identified. A possible mechanism is saturation of transporters at the absorption site or at the hepatobiliary clearance route.

Hydrochlorothiazide

Absorption

The absorption of hydrochlorothiazide, after an oral dose, is rapid (T_{max} about 2 h). 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.

Metabolism and elimination
Hydrochlorothiazide is eliminated predominantly as unchanged compound. 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. There is more than 95% of the absorbed dose being excreted as unchanged compound in the urine. The renal clearance is composed of passive filtration and active secretion into the renal tubule.

Aliskiren/hydrochlorothiazide
Following oral administration of Sprimeo HCT tablets, the median peak plasma concentration time is within 1 hour for aliskiren and 2.5 hours for hydrochlorothiazide.

The rate and extent of absorption of Sprimeo HCT are equivalent to the bioavailability of aliskiren and hydrochlorothiazide when administered as individual monotherapies. Similar food effect was observed for Sprimeo HCT as for the individual monotherapies.

Characteristics in patients
Sprimeo HCT has been shown to be effective as a once-a-day antihypertensive treatment in adult patients, regardless of gender, age, body mass index and ethnicity.

The pharmacokinetics of aliskiren are not significantly affected in patients with mild to moderate liver disease. Consequently, no initial dose adjustment of Sprimeo HCT is required in patients with mild to moderate hepatic impairment. No data are available on patients with severe hepatic impairment treated by Sprimeo HCT. Sprimeo HCT is contraindicated in patients with severe hepatic impairment (see section 4.3).

No adjustment of the initial dose is required for patients with mild to moderate renal impairment (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. Sprimeo HCT is contraindicated in patients with anuria or severe renal impairment (GFR < 30 ml/min/1.73 m^2) and the concomitant use of Sprimeo HCT with ARBs or ACEIs is contraindicated in patients with renal impairment (GFR < 60 ml/min/1.73 m^2) (see section 4.3).

The pharmacokinetics of aliskiren were evaluated in patients with end stage renal disease receiving haemodialysis. Administration of a single oral dose of 300 mg aliskiren was associated with very minor changes in the pharmacokinetics of aliskiren (change in C_{max} of less than 1.2 fold; increase in AUC of up to 1.6 fold) compared to matched healthy subjects. Timing of haemodialysis did not significantly alter the pharmacokinetics of aliskiren in ESRD patients. Therefore, if administration of aliskiren in ESRD patients receiving haemodialysis is considered necessary, no dose adjustment is warranted in these patients. However, the use of aliskiren is not recommended in patients with severe renal impairment (see section 4.4).

No initial dose adjustment of Sprimeo HCT is required in elderly patients. Limited data suggest that the systemic clearance of hydrochlorothiazide is reduced in both healthy and hypertensive elderly subjects compared to young healthy volunteers.

No pharmacokinetic data are available in the paediatric population.

5.3 Preclinical safety data

Safety pharmacology studies with aliskiren did not reveal any adverse effects on central nervous, respiratory or cardiovascular function. Findings during repeat-dose toxicity studies in animals were consistent with the known local irritation potential or the expected pharmacological effects of aliskiren. No carcinogenic potential for aliskiren was detected in a 2-year rat study and a 6-month transgenic mouse study. One colonic adenoma and one caecal adenocarcinoma recorded in rats at the dose of 1,500 mg/kg/day were not statistically significant. Aliskiren was devoid of any mutagenic potential, embryo-foetal toxicity or teratogenicity. Fertility, prenatal development and postnatal development were unaffected in rats.

Preclinical evaluations to support the administration of hydrochlorothiazide in humans included *in vitro* genotoxicity assays and reproductive toxicity and carcinogenicity studies in rodents. Extensive clinical data are available for hydrochlorothiazide and these are reflected in the relevant sections.

The findings observed in the 2-week and 13-week toxicity studies were consistent with those observed previously with aliskiren or hydrochlorothiazide monotherapies. There were no new or unexpected findings observed of relevance to human use. Increased cellular vacuolation of the adrenal gland zona glomerulosa was observed during the 13-week toxicity study in rats. The finding was observed in animals treated with hydrochlorothiazide but not in those animals receiving aliskiren alone or vehicle. There was no evidence that this finding was enhanced in the aliskiren/hydrochlorothiazide combination as it was only apparent at a minimal severity in all animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Cellulose microcrystalline
Crospovidone
Lactose monohydrate
Wheat starch
Povidone
Magnesium stearate
Silica colloidal anhydrous
Talc

Coating:
Talc
Hypromellose
Macrogol
Titanium dioxide (E171)
Red iron oxide (E172)
Black iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

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

PA/Alu/PVC – Alu blisters:
Single-packs containing 7, 14, 28, 30, 50 or 56 tablets.
Multi-packs containing 90, 98 or 280 tablets.

PVC/polychlorotrifluoroethylene (PCTFE) – Alu blisters:
Single-packs containing 7, 14, 28, 30, 50, 56, 90 or 98 tablets.
Single-packs (perforated unit dose blister) containing 56 x 1 tablets.
Multi-packs containing 280 tablets.
Multi-packs (perforated unit dose blister) containing 98 x 1 tablets.

Not all pack sizes or strengths may be marketed.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/683/041-060

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23.06.2011

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Sprimeo HCT 300 mg/25 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 300 mg aliskiren (as hemifumarate) and 25 mg hydrochlorothiazide.

Excipients: Each tablet contains 50 mg lactose monohydrate and 49 mg wheat starch.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Light yellow, biconvex, ovaloid film-coated tablet imprinted with “CVV” on one side and “NVR” on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension in adults.

Sprimeo HCT is indicated in patients whose blood pressure is not adequately controlled on aliskiren or hydrochlorothiazide used alone.

Sprimeo HCT is indicated as substitution therapy in patients adequately controlled with aliskiren and hydrochlorothiazide, given concurrently, at the same dose level as in the combination.

4.2 Posology and method of administration

The recommended dose of Sprimeo HCT is one tablet per day. Sprimeo HCT should be taken with a light meal once a day, preferably at the same time each day. Grapefruit juice should not be taken together with Sprimeo HCT.

The antihypertensive effect is largely manifested within 1 week and the maximum effect is generally seen within 4 weeks.

Posology in patients not adequately controlled with aliskiren or hydrochlorothiazide monotherapy
Individual dose titration with each of the two components may be recommended before changing to the fixed combination. When clinically appropriate, direct change from monotherapy to the fixed combination may be considered.

Sprimeo HCT 300 mg /25 mg may be administered in patients whose blood pressure is not adequately controlled with aliskiren 300 mg or hydrochlorothiazide 25 mg alone or by Sprimeo HCT 300 mg/12.5 mg or Sprimeo HCT 150 mg/25 mg.

If blood pressure remains uncontrolled after 2-4 weeks of therapy, the dose may be titrated up to a maximum of Sprimeo HCT 300 mg/25 mg daily. Dosing should be individualised and adjusted according to the patient’s clinical response.

Posology as substitution therapy
For convenience, patients receiving aliskiren and hydrochlorothiazide from separate tablets may be switched to a fixed combination tablet of Sprimeo HCT containing the same component doses.

Renal impairment
No adjustment of the initial dose is required for patients with mild to moderate renal impairment (see sections 4.4 and 5.2). Due to the hydrochlorothiazide component, Sprimeo HCT is contraindicated for use in patients with anuria and in patients with severe renal impairment (glomerular filtration rate (GFR) < 30 ml/min/1.73 m^2). The concomitant use of Sprimeo HCT with angiotensin II receptor blockers (ARB) or angiotensin converting enzyme inhibitors (ACEI) is contraindicated in patients with renal impairment (GFR < 60 ml/min/1.73 m^2) (see sections 4.3, 4.4 and 5.2).

Hepatic impairment
No adjustment of the initial dose is required for patients with mild to moderate hepatic impairment (see section 5.2). Sprimeo HCT is contraindicated in patients with severe hepatic impairment (see sections 4.3 and 4.4).

Elderly patients (over 65 years)
The recommended starting dose of aliskiren in elderly patients is 150 mg. No clinically meaningful additional blood pressure reduction is observed by increasing the dose to 300 mg in the majority of elderly patients.

Paediatric patients
Sprimeo HCT is not recommended for use in children and adolescents below age 18 due to a lack of data on safety and efficacy (see section 5.2).

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients (see section 6.1), or to other sulphonamide-derived substances.
- History of angioedema with aliskiren.
- Hereditary or idiopathic angioedema.
- Second and third trimesters of pregnancy (see section 4.6).
- Anuria.
- Severe renal impairment (GFR < 30 ml/min/1.73 m^2).
- Refractory hypokalaemia, hyponatraemia, hypercalcaemia and symptomatic hyperuricaemia.
- Severe hepatic impairment.
- The concomitant use of aliskiren with ciclosporin and itraconazole, two highly potent P-glycoprotein (P-gp) inhibitors, and other potent P-gp inhibitors (e.g. quinidine), is contraindicated (see section 4.5).
- The concomitant use of aliskiren with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) (see sections 4.2, 4.4, 4.5 and 5.1).

4.4 Special warnings and precautions for use

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
Hypotension, syncope, stroke, hyperkalaemia, and changes in renal function (including acute renal failure) have been reported in susceptible individuals, especially if combining medicinal products that affect this system (see section 5.1). Dual blockade of the renin-angiotensin-aldosterone system by combining aliskiren with an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin II receptor blocker (ARB) is therefore not recommended.

The use of aliskiren in combination with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) (see section 4.3).

Heart failure
Aliskiren should be used with caution in patients with serious congestive heart failure (New York Heart Association (NYHA) functional class III-IV). Sprimeo HCT should be used with caution in patients with heart failure due to limited clinical efficacy and safety data.

Angioedema
As with other agents acting on the renin-angiotensin system, angioedema or symptoms suggestive of angioedema (swelling of the face, lips, throat and/or tongue) have been reported in patients treated with aliskiren.

A number of these patients had a history of angioedema or symptoms suggestive of angioedema, which in some cases followed use of other medicines that can cause angioedema, including RAAS blockers (angiotensin converting enzyme inhibitors or angiotensin receptor blockers) (see section 4.8).

Patients with a history of angioedema may be at increased risk of experiencing angioedema during treatment with aliskiren (see sections 4.3 and 4.8). Caution should therefore be exercised when prescribing aliskiren to patients with a history of angioedema, and such patients should be closely monitored during treatment (see section 4.8) especially at the beginning of the treatment.

If angioedema occurs, Sprimeo HCT should be promptly discontinued and appropriate therapy and monitoring provided until complete and sustained resolution of signs and symptoms has occurred. Where there is involvement of the tongue, glottis or larynx adrenaline should be administered. In addition, measures necessary to maintain patent airways should be provided.

Sodium- and/or volume-depleted patients
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 Sprimeo HCT. Sprimeo HCT should be used only after correction of any pre-existing sodium and/or volume depletion.

Electrolyte imbalance
Treatment with Sprimeo 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 Sprimeo HCT should be discontinued until stable correction of the potassium balance. Although hypokalaemia may develop with the use of thiazide diuretics, concurrent therapy with aliskiren may reduce diuretic-induced hypokalaemia. The risk of hypokalaemia is greater in patients with cirrhosis of the liver, patients experiencing brisk diuresis, patients with inadequate oral electrolyte intake and patients receiving concomitant therapy with corticosteroids or adrenocorticotropic hormone (ACTH) (see sections 4.5 and 4.8).

Conversely, increases in serum potassium have been observed with aliskiren in post-marketing experience and these may be exacerbated by concomitant use of other agents acting on the RAAS or by non-steroidal anti-inflammatory drugs (NSAIDs). Consistent with standard medical practice, periodic determination of renal function including serum electrolytes is advised if co-administration is considered necessary. The concomitant use of aliskiren and ACEIs or ARBs is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) (see sections 4.3, 4.5 and 4.8).

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 Sprimeo HCT therapy, the treatment should be discontinued until normalisation of natraemia.

There is no evidence that Sprimeo HCT would reduce or prevent diuretic-induced hyponatraemia. Chloride deficit is generally mild and usually does not require treatment.

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

Thiazides reduce urinary calcium excretion and may cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Sprimeo HCT is contraindicated in patients with hypercalcaemia and should only be used after correction of any pre-existing hypercalcaemia. Sprimeo 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.

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

No dosage adjustment is necessary in patients with mild to moderate renal impairment (GFR $\geq$ 30 ml/min/1.73 m^2).

There is no experience regarding the administration of Sprimeo HCT in patients who have recently undergone kidney transplantation.

As for other agents acting on the renin-angiotensin system, caution should be exercised when aliskiren is given in the presence of conditions pre-disposing to kidney dysfunction such as hypovolaemia (e.g. due to blood loss, severe or prolonged diarrhoea, prolonged vomiting, etc.), heart disease, liver disease, diabetes mellitus or kidney disease. The concomitant use of aliskiren and ACEIs or ARBs is contraindicated in patients with renal impairment (GFR < 60 ml/min/1.73 m^2). Acute renal failure, reversible upon discontinuation of treatment, has been reported in at-risk patients receiving aliskiren in post-marketing experience. In the event that any signs of renal failure occur, aliskiren should be promptly discontinued.

Hepatic impairment
Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. No adjustment of the initial dose is required for patients with mild to moderate hepatic impairment. No data are available for the use of Sprimeo HCT in patients with severe hepatic impairment. Due to the hydrochlorothiazide component, Sprimeo HCT is contraindicated in patients with severe hepatic impairment (see sections 4.3 and 5.2).

There is no clinical experience with Sprimeo HCT in patients with hepatic impairment.

Moderate P-gp inhibitors
Co-administration of aliskiren 300 mg with ketoconazole 200 mg or verapamil 240 mg resulted in a 76% or 97% increase in aliskiren AUC, respectively. Therefore caution should be exercised when aliskiren is administered with moderate P-gp inhibitors such as ketoconazole or verapamil (see section 4.5).

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy
As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Renal artery stenosis and renovascular hypertension
No controlled clinical data are available on the use of Sprimeo HCT in patients with unilateral or bilateral renal artery stenosis, or stenosis to a solitary kidney. However, as with other agents acting on the renin-angiotensin system, there is an increased risk of renal insufficiency, including acute renal failure, when patients with renal artery stenosis are treated with aliskiren. Therefore caution should be exercised in these patients. If renal failure occurs, treatment should be discontinued.

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

Metabolic and endocrine effects
Thiazide diuretics, including hydrochlorothiazide, may alter glucose tolerance and raise serum levels of cholesterol and triglycerides, and uric acid. In diabetic patients dosage adjustments of insulin or oral hypoglycaemic agents may be required. Concomitant use of Sprimeo HCT with ARBs or ACEIs is contraindicated in patients with diabetes mellitus (see section 4.3).

Due to the hydrochlorothiazide component, Sprimeo HCT is contraindicated in symptomatic hyperuricaemia (see section 4.3). 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 an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Sprimeo HCT is contraindicated in patients with hypercalcaemia and should only be used after correction of any pre-existing hypercalcaemia. Sprimeo 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 Sprimeo HCT, it is recommended to stop the treatment. If a re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Acute angle-closure glaucoma
Hydrochlorothiazide, a sulphonamide, has been associated with an idiosyncratic reaction resulting in 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 weeks 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
In the event of severe and persistent diarrhoea, Sprimeo HCT therapy should be stopped.

As with any antihypertensive agent, excessive reduction of blood pressure in patients with ischaemic cardiopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke.

Hypersensitivity reactions to hydrochlorothiazide may occur in patients, but are more likely in patients with allergy and asthma.

Excipients
Sprimeo HCT contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sprimeo HCT contains wheat starch. It is suitable for people with coeliac disease. Patients with wheat allergy (different from coeliac disease) should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Information on Sprimeo HCT interactions
Medicinal products affecting serum potassium levels: The potassium-depleting effect of hydrochlorothiazide is attenuated by the potassium-sparing effect of aliskiren. However, this effect of hydrochlorothiazide on serum potassium would be expected to be potentiated by other medicinal products associated with potassium loss and hypokalaemia (e.g. other kaliuretic diuretics, corticosteroids, laxatives, adrenocorticotropic hormone (ACTH), amphotericin, carbenoxolone, penicillin G, salicylic acid derivatives). Conversely, concomitant use of other agents affecting the RAAS, of NSAIDs or of agents that increase serum potassium levels (e.g. potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, heparin) may lead to increases in serum potassium. If co-medication with an agent affecting the level of serum potassium is considered necessary, caution is advisable. The combination of aliskiren with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) and is not recommended in other patients (see sections 4.3, 4.4 and 5.1).

Medicinal products affected by serum potassium disturbances: Periodic monitoring of serum potassium is recommended when Sprimeo HCT is administered with medicinal products affected by serum potassium disturbances (e.g. digitalis glycosides, antiarrhythmics).

Non-steroidal anti-inflammatory drugs (NSAIDs), including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors), acetylsalicylic acid and non-selective NSAIDs: As with other agents acting on the renin-angiotensin system, NSAIDs may reduce the anti-hypertensive effect of aliskiren. NSAIDs may also weaken the diuretic and antihypertensive activity of hydrochlorothiazide.

In some patients with compromised renal function (dehydrated patients or elderly patients) aliskiren and hydrochlorothiazide given concomitantly with NSAIDs may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore the use of Sprimeo HCT with an NSAID requires caution, especially in elderly patients.

Other antihypertensive agents: The antihypertensive effect of Sprimeo HCT may be increased with the concomitant use of other antihypertensive agents.

Additional information on aliskiren interactions
The combination of aliskiren with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) and is not recommended in other patients (see sections 4.3, 4.4 and 5.1).

Compounds that have been investigated in aliskiren clinical pharmacokinetic studies include acenocoumarol, atenolol, celecoxib, fenofibrate, pioglitazone, allopurinol, isosorbide-5-mononitrate, digoxin, metformin, amlodipine, atorvastatin, cimetidine and hydrochlorothiazide. No clinically relevant interactions have been identified. As a result no dose adjustment for aliskiren or these co-administered medicinal products is necessary.

P-glycoprotein interactions: MDR1/Mdr1a/1b (P-gp) was found to be the major efflux system involved in intestinal absorption and biliary excretion of aliskiren in preclinical studies. Rifampicin, which is an inducer of P-gp, reduced aliskiren bioavailability by approximately 50% in a clinical study. Other inducers of P-gp (St. John's wort) might decrease the bioavailability of aliskiren. Although this has not been investigated for aliskiren, it is known that P-gp also controls tissue uptake of a variety of substrates and P-gp inhibitors can increase the tissue-to-plasma concentration ratios. Therefore, P-gp inhibitors may increase tissue levels more than plasma levels. The potential for drug interactions at the P-gp site will likely depend on the degree of inhibition of this transporter.

P-gp potent inhibitors: A single dose drug interaction study in healthy subjects has shown that ciclosporin (200 and 600 mg) increases C_{max} of aliskiren 75 mg approximately 2.5-fold and AUC approximately 5-fold. The increase may be higher with higher aliskiren doses. In healthy subjects, itraconazole (100 mg) increases AUC and C_{max} of aliskiren (150 mg) by 6.5-fold and 5.8-fold, respectively. Therefore, concomitant use of aliskiren and P-gp potent inhibitors is contraindicated (see section 4.3).

Moderate P-gp inhibitors: Co-administration of ketoconazole (200 mg) or verapamil (240 mg) with aliskiren (300 mg) resulted in a 76% or 97% increase in aliskiren AUC, respectively. The change in plasma levels of aliskiren in the presence of ketoconazole or verapamil is expected to be within the range that would be achieved if the dose of aliskiren were doubled; aliskiren doses of up to 600 mg, or twice the highest recommended therapeutic dose, have been found to be well tolerated in controlled clinical trials. Preclinical studies indicate that aliskiren and ketoconazole co-administration enhances aliskiren gastrointestinal absorption and decreases biliary excretion. Therefore, caution should be exercised when aliskiren is administered with ketoconazole, verapamil or other moderate P-gp inhibitors (clarithromycin, telithromycin, erythromycin, amiodarone).

P-gp substrates or weak inhibitors: No relevant interactions with atenolol, digoxin, amlodipine or cimetidine have been observed. When administered with atorvastatin (80 mg), steady-state aliskiren (300 mg) AUC and C_{max} increased by 50%.

Organic anion transporting polypeptide (OATP) inhibitors: Preclinical studies indicate that aliskiren might be a substrate of organic anion transporting polypeptides. Therefore, the potential exists for interactions between OATP inhibitors and aliskiren when administered concomitantly (see interaction with Grapefruit juice).

Grapefruit juice: Administration of grapefruit juice with aliskiren resulted in a decrease in AUC and C_{max} of aliskiren. Co-administration with aliskiren 150 mg resulted in a 61% decrease in aliskiren AUC and co-administration with aliskiren 300 mg resulted in a 38% decrease in aliskiren AUC. This decrease is likely due to an inhibition of organic anion transporting polypeptide-mediated uptake of aliskiren by grapefruit juice in the gastrointestinal tract. Therefore, because of the risk of therapeutic failure, grapefruit juice should not be taken together with Sprimeo HCT.

Furosemide: When aliskiren was co-administered with furosemide, the AUC and C_{max} of furosemide were reduced by 28% and 49%, respectively. It is therefore recommended to monitor the effects when initiating and adjusting furosemide therapy to avoid possible underutilisation in clinical situations of volume overload.

Warfarin: The effects of aliskiren on warfarin pharmacokinetics have not been evaluated.

Food interactions: Meals with a high fat content have been shown to reduce the absorption of aliskiren substantially.

Additional information on hydrochlorothiazide interactions
When administered concurrently, the following medicinal products may interact with thiazide diuretics:

Lithium: Renal clearance of lithium is reduced by thiazides, therefore the risk of lithium toxicity may be increased with hydrochlorothiazide. Co-administration of lithium and hydrochlorothiazide is not recommended. If this combination proves essential, careful monitoring of serum lithium level is recommended during concomitant use.

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 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.

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.

Digoxine or other digitalis glycosides: Thiazide-induced hypokalaemia or hypomagnesaemia may occur as undesirable effects, favouring the onset of digitalis-induced cardiac arrhythmias.

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.

Antidiabetic agents (e.g. insulin and oral antidiabetic agents): Thiazides may alter glucose tolerance. Dose adjustment of the antidiabetic medicinal product may be necessary (see section 4.4). 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.

Medicinal products used in the treatment of gout: 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.

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.

Amantadine: Thiazides, including hydrochlorothiazide, may increase the risk of adverse reactions caused by amantadine.

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.

Cytotoxic agents: Thiazides, including hydrochlorothiazide, may reduce the renal excretion of cytotoxic agents (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.

Non-depolarising skeletal muscle relaxants: Thiazides, including hydrochlorothiazide, potentiate the action of skeletal muscle relaxants such as curare derivatives.

Alcohol, barbiturates or narcotics: Concomitant administration of thiazide diuretics with subtances that also have a blood pressure lowering effect (e.g. by reducing sympathetic central nervous system activity or direct vasodilatation) may potentiate orthostatic hypotension.

Methyldopa: There have been isolated reports of haemolytic anaemia occurring with concomitant use of hydrochlorothiazide and methyldopa.

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 rehydrated before administration.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data on the use of aliskiren in pregnant women. Aliskiren was not teratogenic in rats or rabbits (see section 5.3). Other substances that act directly on the RAAS have been associated with serious foetal malformations and neonatal death when used during second and third trimesters. 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.

Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or pre-eclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.

Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

No specific clinical studies have been performed with this combination, therefore Sprimeo HCT should not be used during the first trimester of pregnancy or in women planning to become pregnant and is contraindicated during the second and third trimesters (see section 4.3). A switch to a suitable alternative treatment should be carried out in advance of a planned pregnancy. If pregnancy is detected during therapy, Sprimeo HCT should be discontinued as soon as possible.

Breast-feeding
It is not known whether aliskiren is excreted in human milk. Aliskiren was secreted in the milk of lactating rats.

Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit milk production.

The use of Sprimeo HCT during breast-feeding is not recommended. If Sprimeo HCT is used during breast-feeding, doses should be kept as low as possible.

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed. Sprimeo HCT is unlikely to affect the ability to drive and use machines. However, when driving vehicles or operating machinery it must be borne in mind that dizziness or drowsiness may occasionally occur when taking antihypertensive therapy.

4.8 Undesirable effects

Aliskiren/hydrochlorothiazide combination
The safety of Sprimeo HCT has been evaluated in 9 clinical trials with more than 3,900 patients, including over 700 treated for over 6 months, and 190 for over 1 year. The incidence of adverse reactions showed no association with gender, age, body mass index, race or ethnicity. Treatment with Sprimeo HCT had an overall incidence of adverse experiences at doses up to 300 mg/25 mg similar to placebo. Adverse reactions have generally been mild and transient in nature and have only infrequently required discontinuation of therapy. The most common adverse drug reaction observed with Sprimeo HCT is diarrhoea. The adverse drug reactions previously reported with one of the individual components of Sprimeo HCT (aliskiren and hydrochlorothiazide) and listed in the respective paragraphs on the individual components may occur with Sprimeo HCT.

The frequency of adverse reactions listed below is defined using the following convention: 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) and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Gastrointestinal disorders	
Common:	Diarrhoea

Diarrhoea: Diarrhoea is a dose-related adverse drug reaction for aliskiren. In controlled clinical trials, the incidence of diarrhoea in Sprimeo HCT-treated patients was 1.3% compared to 1.4% for aliskiren- or 1.9% for hydrochlorothiazide-treated patients.

Serum potassium: In a large placebo-controlled clinical trial, the opposite effects of aliskiren (150 mg or 300 mg) and hydrochlorothiazide (12.5 mg or 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 potassium to detect possible electrolyte imbalance should be performed in patients at risk at appropriate intervals (see sections 4.4 and 4.5).

Additional information on individual components
Other adverse reactions previously reported with one of the individual components may occur with Sprimeo HCT even if not observed in clinical trials.

Aliskiren
Treatment with Aliskiren up to 300 mg resulted in an overall incidence of adverse reactions similar to placebo. Adverse reactions have generally been mild and transient in nature and have only infrequently required discontinuation of therapy. The most common adverse drug reaction is diarrhoea.

The known aliskiren adverse drug reactions are presented in the table below using the same convention as described previously for the fixed combination.

Nervous system disorders		
	Common:	Dizziness
Vascular disorders		
	Uncommon:	Hypotension
Gastrointestinal disorders		
	Common:	Diarrhoea
Immune system disorders		
	Rare:	Hypersensitivity reactions
Skin and subcutaneous tissue disorders		
	Uncommon:	Rash, severe cutaneous adverse reactions (SCARs) including toxic epidermal necrolysis (TEN) and oral mucosal reactions
	Rare:	Angioedema
Musculoskeletal and connective tissue disorders		
	Common:	Arthralgia
Renal and urinary disorders		
	Uncommon:	Acute renal failure, renal impairment
General disorders and administration site conditions		
	Uncommon:	Oedema peripheral
Investigations		
	Common:	Hyperkalaemia
	Rare:	Haemoglobin decreased, haematocrit decreased
	Rare:	Blood creatinine increased

Angioedema and hypersensitivity reactions have occurred during treatment with aliskiren. In controlled clinical trials, angioedema and hypersensitivity reactions occurred rarely during treatment with aliskiren with rates comparable to treatment with placebo or comparators.

Cases of angioedema or symptoms suggestive of angioedema (swelling of the face, lips, throat and/or tongue) have also been reported in post-marketing experience. A number of these patients had a history of angioedema or symptoms suggestive of angioedema which in some cases was associated with the administration of other medicines known to cause angioedema, including RAAS blockers (ACE inhibitors or ARBs).

Hypersensitivity reactions have also been reported in post-marketing experience.

In the event of any signs suggesting a hypersensitivity reaction/angioedema (in particular difficulties in breathing or swallowing, rash, itching, hives or swelling of the face, extremities, eyes, lips and/or tongue, dizziness) patients should discontinue treatment and contact the physician (see section 4.4).

Arthralgia has been reported in post-marketing experience. In some cases this occurred as part of a hypersensitivity reaction.

Haemoglobin and haematocrit: Small decreases in haemoglobin and haematocrit (mean decreases of approximately 0.05 mmol/l and 0.16 volume percent, respectively) were observed. No patients discontinued therapy due to anaemia. This effect is also seen with other agents acting on the renin-angiotensin system, such as ACEI and ARBs.

Serum potassium: Increases in serum potassium have been observed with aliskiren and these may be exacerbated by concomitant use of other agents acting on the RAAS or by NSAIDs. Consistent with standard medical practice, periodic determination of renal function including serum electrolytes is advised if co-administration is considered necessary. The combination of aliskiren with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) and is not recommended in other patients (see sections 4.3, 4.4 and 5.1).

In post-marketing experience, renal dysfunction and cases of acute renal failure have been reported in patients at risk (see section 4.4). There have also been reports of peripheral oedema, increase in blood creatinine and severe cutaneous adverse reactions (SCARs) including toxic epidermal necrolysis (TEN) and oral mucosal reactions.

Hydrochlorothiazide
Hydrochlorothiazide has been extensively prescribed for many years, frequently in higher doses than those contained in Sprimeo HCT. The following adverse reactions have been reported in patients treated with thiazide diuretics alone, including hydrochlorothiazide:

Blood and lymphatic system disorders		
	Rare:	Thrombocytopenia sometimes with purpura
	Very rare:	Agranulocytosis, bone marrow depression, haemolytic anaemia, leucopenia
	Not known:	Aplastic anaemia
Immune system disorders		
	Very rare:	Hypersensitivity
Metabolism and nutrition disorders		
	Very common:	Hypokalaemia
	Common:	Hyperuricaemia, hypomagnesaemia, hyponatraemia
	Rare:	Hypercalcaemia, hyperglycaemia, worsening of diabetic metabolic state
	Very rare:	Hypochloraemic alkalosis
Psychiatric disorders		
	Rare:	Depression, sleep disturbances
Nervous system disorders		
	Rare:	Dizziness, headache, paraesthesia
Eye disorders		
	Rare:	Visual impairment
	Not known:	Acute angle-closure glaucoma
Cardiac disorders		
	Rare:	Cardiac arrhythmias
Vascular disorders		
	Common:	Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders		
	Very rare:	Respiratory distress (including pneumonitis and pulmonary oedema)
Gastrointestinal disorders		
	Common:	Decreased appetite, mild nausea and vomiting
	Rare:	Abdominal discomfort, constipation, diarrhoea
	Very rare:	Pancreatitis
Hepatobiliary disorders		
	Rare:	Intrahepatic cholestasis, jaundice
Skin and subcutaneous tissue disorders		
	Common:	Urticaria and other forms of rash
	Rare:	Photosensitivity reactions
	Very rare:	Cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, vasculitis necrotising and toxic epidermal necrolysis
	Not known:	Erythema multiforme
Musculoskeletal and connective tissue disorders		
	Not known:	Muscle spasm
Renal and urinary disorders		
	Not known:	Renal dysfunction, acute renal failure

Reproductive system and breast disorders		
	Common:	Impotence
General disorders and administration site conditions		
	Not known:	Asthenia, pyrexia
Investigations		
	Very common:	Increases in cholesterol and triglycerides
	Rare:	Glycosuria

4.9 Overdose

No information is available on the treatment of overdose with Sprimeo HCT. The most likely manifestation of overdose would be hypotension, related to the antihypertensive effect of aliskiren.

Overdose with hydrochlorothiazide is associated with electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration 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 cardiac arrhythmias associated with the concomitant use of digitalis glycosides or certain antiarrhythmic medicinal products. If symptomatic hypotension should occur, supportive treatment should be initiated.

In a study conducted in patients with end stage renal disease (ESRD) receiving haemodialysis, dialysis clearance of aliskiren was low (< 2% of oral clearance). Therefore dialysis is not adequate to treat aliskiren over-exposure.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Renin inhibitor (aliskiren) combinations with diuretics (hydrochlorothiazide), ATC code: C09XA52
Sprimeo HCT combines two antihypertensive compounds to control blood pressure in patients with essential hypertension: Aliskiren belongs to the class of direct renin inhibitors and hydrochlorothiazide to the class of thiazide diuretics. The combination of these substances with complementary mechanisms of action provides an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Aliskiren
Aliskiren is an orally active, non-peptide, potent and selective direct inhibitor of human renin.

By inhibiting the enzyme renin, aliskiren inhibits the RAAS at the point of activation, blocking the conversion of angiotensinogen to angiotensin I and decreasing levels of angiotensin I and angiotensin II. Whereas other agents that inhibit the RAAS (angiotensin converting enzyme inhibitors (ACEI) and angiotension II receptor blockers (ARB)) cause a compensatory rise in plasma renin activity (PRA), treatment with aliskiren decreases PRA in hypertensive patients by approximately 50 to 80%. Similar reductions were found when aliskiren was combined with other antihypertensive agents. The clinical implications of the effects on PRA are not known at the present time.

In hypertensive patients, once-daily administration of aliskiren at doses of 150 mg and 300 mg provided dose-dependent reductions in both systolic and diastolic blood pressure that were maintained over the entire 24-hour dose interval (maintaining benefit in the early morning) with a mean peak to trough ratio for diastolic response of up to 98% for the 300 mg dose. 85 to 90% of the maximal blood-pressure-lowering effect was observed after 2 weeks. The blood-pressure-lowering effect was sustained during long-term treatment (12 months), and was independent of age, gender, body mass index and ethnicity.

Combination therapy studies are available for aliskiren added to the diuretic hydrochlorothiazide, the calcium channel blocker amlodipine and the beta blocker atenolol. These combinations were efficacious and well tolerated.

The efficacy and safety of aliskiren-based therapy were compared to ramipril-based therapy in a 9-month non-inferiority study in 901 elderly patients (≥ 65 years) with essential systolic hypertension. Aliskiren 150 mg or 300 mg per day or ramipril 5 mg or 10 mg per day were administered for 36 weeks with optional add-on therapy of hydrochlorothiazide (12.5 mg or 25 mg) at week 12, and amlodipine (5 mg or 10 mg) at week 22. Over the 12 week period, aliskiren monotherapy lowered systolic/diastolic blood pressure by 14.0/5.1 mmHg, compared to 11.6/3.6 mmHg for ramipril, consistent with aliskiren being non-inferior to ramipril at the dosages chosen and the differences in systolic and diastolic blood pressure were statistically significant. Tolerability was comparable in both treatment arms, however cough was more often reported with the ramipril regimen than the aliskiren regimen (14.2% vs. 4.4%), whilst diarrhoea was more common with the aliskiren regimen than for the ramipril regimen (6.6% vs. 5.0%).

In a 8-week study in 754 hypertensive elderly (≥ 65 years) and very elderly patients (30% ≥ 75 years) aliskiren at doses of 75 mg, 150 mg and 300 mg provided statistically significant superior reduction in blood pressure (both systolic and diastolic) when compared to placebo. No additional blood pressure lowering effect was detected with 300 mg aliskiren compared to 150 mg aliskiren. All three doses were well tolerated in both elderly and very elderly patients.

There has been no evidence of first-dose hypotension and no effect on pulse rate in patients treated in controlled clinical studies. With cessation of treatment, blood pressure gradually returned towards baseline levels over a period of several weeks, with no evidence of a rebound effect for blood pressure or PRA.

In a 36-week study involving 820 patients with ischaemic left ventricular dysfunction, no changes in ventricular remodelling as assessed by left ventricular end systolic volume were detected with aliskiren compared to placebo on top of background therapy.

The combined rates of cardiovascular death, hospitalisation for heart failure, recurrent heart attack, stroke and resuscitated sudden death were similar in the aliskiren group and the placebo group. However, in patients receiving aliskiren there was a significantly higher rate of hyperkalaemia, hypotension and kidney dysfunction when compared to the placebo group.

Aliskiren was evaluated for cardiovascular and/or renal benefit in a double-blind placebo controlled randomised trial in 8,606 patients with type 2 diabetes and chronic kidney disease (evidenced by proteinuria and/or GFR < 60 ml/min/1.73 m^2) with or without cardiovascular disease. In most patients arterial blood pressure was well controlled at baseline. The primary endpoint was a composite of cardiovascular and renal complications.

In this study, aliskiren 300 mg was compared to placebo when added to standard of care which included either an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker. The study was discontinued prematurely because the participants were unlikely to benefit from aliskiren. Preliminary study results indicated a hazard ratio for the primary endpoint of 1.09 in favour of placebo (95% Confidence Interval: 0.97, 1.22, 2-sided p=0.17). In addition, an increased incidence of serious adverse outcomes was observed with aliskiren compared to placebo for renal complications (4.7% versus 3.3%), hyperkalaemia (36.9% versus 27.1%), hypotension (18.4% versus 14.6%) and stroke (2.7% versus 2.0%). The increased incidence of non-fatal stroke was greater in patients with renal insufficiency.

Hydrochlorothiazide
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 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.

Aliskiren/hydrochlorothiazide
Over 3,900 hypertensive patients received Sprimeo HCT once daily in clinical trials.

In hypertensive patients, once-daily administration of Sprimeo HCT provided dose-dependent reductions in both systolic and diastolic blood pressure that were maintained over the entire 24-hour dose interval. The antihypertensive effect is largely manifested within 1 week and the maximum effect is generally seen within 4 weeks.The blood-pressure-lowering effect was sustained during long-term treatment, and was independent of age, gender, body mass index and ethnicity. The antihypertensive effect of a single dose of the combination persisted for 24 hours. Upon withdrawal of the aliskiren treatment (aliskiren with or without hydrochlorothiazide add-on), the return of blood pressure towards baseline was gradual (3-4 weeks) with no evidence of the rebound effect.

Sprimeo HCT was studied in a placebo-controlled trial including 2,762 hypertensive patients with diastolic blood pressure ≥ 95 mmHg and < 110 mmHg (mean baseline blood pressure of 153.6/99.2 mmHg). In this study, Sprimeo HCT in doses from 150 mg/12.5 mg to 300 mg/25 mg produced dose-dependent blood pressure reductions (systolic/diastolic) from 17.6/11.9 mmHg to 21.2/14.3 mmHg, respectively, compared to 7.5/6.9 mmHg with placebo. The greater blood pressure reductions with these combination doses were also significantly greater than the respective doses of aliskiren and hydrochlorothiazide when used alone. The combination of aliskiren and hydrochlorothiazide neutralised the reactive increase of PRA caused by hydrochlorothiazide.

When administered in hypertensive patients with markedly elevated blood pressure (systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 100 mmHg), Sprimeo HCT in doses from 150 mg/12.5 mg to 300 mg/25 mg administered without up-titration from monotherapy demonstrated significantly greater systolic/diastolic blood pressure control rates (< 140/90 mmHg) as compared to the respective monotherapies. In this population, Sprimeo HCT 150 mg/12.5 mg to 300 mg/25 mg provided dose-dependent systolic/diastolic blood pressure reduction from 20.6/12.4 mmHg to 24.8/14.5 mmHg, which were significantly superior to the respective monotherapies. The safety of the combination therapy was similar to the respective monotherapies regardless of severity of hypertension or of the presence or absence of additional cardiovascular risk. Hypotension and related adverse events were uncommon with the combination treatment, with no increased incidence in elderly patients.

In a study in 880 randomised patients not adequately responsive to aliskiren 300 mg treatment, the combination of aliskiren/hydrochlorothiazide 300 mg/25 mg produced systolic/diastolic blood pressure reductions of 15.8/11.0 mmHg, which were significantly greater than aliskiren 300 mg monotherapy. In a study in 722 randomised patients not adequately responsive to hydrochlorothiazide 25 mg treatment, the combination of aliskiren/hydrochlorothiazide 300 mg/25 mg produced systolic/diastolic blood pressure reductions of 16.78/10.7 mmHg, which were significantly greater than hydrochlorothiazide 25 mg monotherapy.

In another clinical trial, the efficacy and safety of Sprimeo HCT were also assessed in 489 obese hypertensive patients who did not respond to hydrochlorothiazide 25 mg (baseline systolic/diastolic blood pressure 149.4/96.8 mmHg). In this difficult-to-treat population, Sprimeo HCT provided a blood pressure reduction (systolic/diastolic) of 15.8/11.9 mmHg compared to 15.4/11.3 mmHg for irbesartan/hydrochlorothiazide, 13.6/10.3 mmHg for amlodipine/hydrochlorothiazide and 8.6/7.9 mmHg for hydrochlorothiazide monotherapy, with similar safety to hydrochlorothiazide monotherapy.

In a study in 183 randomised patients with severe hypertension (mean sitting diastolic blood pressure ≥ 105 and < 120 mmHg), aliskiren treatment regimen with optional addition of hydrochlorothiazide 25 mg was shown to be safe and efficacious in reducing blood pressure.

5.2 Pharmacokinetic properties

Aliskiren

Absorption

Following oral absorption, peak plasma concentrations of aliskiren are reached after 1-3 hours. The absolute bioavailability of aliskiren is approximately 2-3%. Meals with a high fat content reduce C_{max} by 85% and AUC by 70%. Steady-state-plasma concentrations are reached within 5-7 days following once-daily administration and steady-state levels are approximately 2-fold greater than with the initial dose.

Distribution

Following intravenous administration, the mean volume of distribution at steady state is approximately 135 litres, indicating that aliskiren distributes extensively into the extravascular space. Aliskiren plasma protein binding is moderate (47-51%) and independent of the concentration.

Metabolism and elimination

The mean half-life is about 40 hours (range 34-41 hours). Aliskiren is mainly eliminated as unchanged compound in the faeces (oral radioactive dose recovery = 91%). Approximately 1.4% of the total oral dose is metabolised. The enzyme responsible for this metabolism is CYP3A4. Approximately 0.6% of the dose is recovered in urine following oral administration. Following intravenous administration, the mean plasma clearance is approximately 9 l/h.

Linearity

Exposure to aliskiren increased slightly more than in proportion to the increase in dose. After single dose administration in the dose range of 75 to 600 mg, a 2-fold increase in dose results in a ~2.3 and 2.6-fold increase in AUC and C_{max}, respectively. Mechanisms responsible for the deviation from dose proportionality have not been identified. A possible mechanism is saturation of transporters at the absorption site or at the hepatobiliary clearance route.

Hydrochlorothiazide

Absorption

The absorption of hydrochlorothiazide, after an oral dose, is rapid (T_{max} about 2 h). 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.

Metabolism and elimination
Hydrochlorothiazide is eliminated predominantly as unchanged compound. 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. There is more than 95% of the absorbed dose being excreted as unchanged compound in the urine. The renal clearance is composed of passive filtration and active secretion into the renal tubule.

Aliskiren/hydrochlorothiazide
Following oral administration of Sprimeo HCT tablets, the median peak plasma concentration time is within 1 hour for aliskiren and 2.5 hours for hydrochlorothiazide.

The rate and extent of absorption of Sprimeo HCT are equivalent to the bioavailability of aliskiren and hydrochlorothiazide when administered as individual monotherapies. Similar food effect was observed for Sprimeo HCT as for the individual monotherapies.

Characteristics in patients
Sprimeo HCT has been shown to be effective as a once-a-day antihypertensive treatment in adult patients, regardless of gender, age, body mass index and ethnicity.

The pharmacokinetics of aliskiren are not significantly affected in patients with mild to moderate liver disease. Consequently, no initial dose adjustment of Sprimeo HCT is required in patients with mild to moderate hepatic impairment. No data are available on patients with severe hepatic impairment treated by Sprimeo HCT. Sprimeo HCT is contraindicated in patients with severe hepatic impairment (see section 4.3).

No adjustment of the initial dose is required for patients with mild to moderate renal impairment (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. Sprimeo HCT is contraindicated in patients with anuria or severe renal impairment (GFR < 30 ml/min/1.73 m^2) and the concomitant use of Sprimeo HCT with ARBs or ACEIs is contraindicated in patients with renal impairment (GFR < 60 ml/min/1.73 m^2) (see section 4.3).

The pharmacokinetics of aliskiren were evaluated in patients with end stage renal disease receiving haemodialysis. Administration of a single oral dose of 300 mg aliskiren was associated with very minor changes in the pharmacokinetics of aliskiren (change in C_{max} of less than 1.2 fold; increase in AUC of up to 1.6 fold) compared to matched healthy subjects. Timing of haemodialysis did not significantly alter the pharmacokinetics of aliskiren in ESRD patients. Therefore, if administration of aliskiren in ESRD patients receiving haemodialysis is considered necessary, no dose adjustment is warranted in these patients. However, the use of aliskiren is not recommended in patients with severe renal impairment (see section 4.4).

No initial dose adjustment of Sprimeo HCT is required in elderly patients. Limited data suggest that the systemic clearance of hydrochlorothiazide is reduced in both healthy and hypertensive elderly subjects compared to young healthy volunteers.

No pharmacokinetic data are available in the paediatric population.

5.3 Preclinical safety data

Safety pharmacology studies with aliskiren did not reveal any adverse effects on central nervous, respiratory or cardiovascular function. Findings during repeat-dose toxicity studies in animals were consistent with the known local irritation potential or the expected pharmacological effects of aliskiren. No carcinogenic potential for aliskiren was detected in a 2-year rat study and a 6-month transgenic mouse study. One colonic adenoma and one caecal adenocarcinoma recorded in rats at the dose of 1,500 mg/kg/day were not statistically significant. Aliskiren was devoid of any mutagenic potential, embryo-foetal toxicity or teratogenicity. Fertility, prenatal development and postnatal development were unaffected in rats.

Preclinical evaluations to support the administration of hydrochlorothiazide in humans included *in vitro* genotoxicity assays and reproductive toxicity and carcinogenicity studies in rodents. Extensive clinical data are available for hydrochlorothiazide and these are reflected in the relevant sections.

The findings observed in the 2-week and 13-week toxicity studies were consistent with those observed previously with aliskiren or hydrochlorothiazide monotherapies. There were no new or unexpected findings observed of relevance to human use. Increased cellular vacuolation of the adrenal gland zona glomerulosa was observed during the 13-week toxicity study in rats. The finding was observed in animals treated with hydrochlorothiazide but not in those animals receiving aliskiren alone or vehicle. There was no evidence that this finding was enhanced in the aliskiren/hydrochlorothiazide combination as it was only apparent at a minimal severity in all animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Cellulose microcrystalline
Crospovidone
Lactose monohydrate
Wheat starch
Povidone
Magnesium stearate
Silica colloidal anhydrous
Talc

Coating:
Talc
Hypromellose
Macrogol
Titanium dioxide (E171)
Red iron oxide (E172)
Yellow iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

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

PA/Alu/PVC – Alu blisters:
Single-packs containing 7, 14, 28, 30, 50 or 56 tablets.
Multi-packs containing 90, 98 or 280 tablets.

PVC/polychlorotrifluoroethylene (PCTFE) – Alu blisters:
Single-packs containing 7, 14, 28, 30, 50, 56, 90 or 98 tablets.
Single-packs (perforated unit dose blister) containing 56 x 1 tablets.
Multi-packs containing 280 tablets.
Multi-packs (perforated unit dose blister) containing 98 x 1 tablets.

Not all pack sizes or strengths may be marketed.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/683/061-080

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23.06.2011

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Novartis Farma S.p.A.
Via Provinciale Schito 131
IT-80058 Torre Annunziata/NA
Italy

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the Marketing Authorisation, is in place and functioning before and whilst the medicinal product is on the market.

Risk Management Plan (RMP)
The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the RMP presented in Module 1.8.2 of the Marketing Authorisation and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency.

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

- **OBLIGATION TO CONDUCT POST-AUTHORISATION MEASURES**

The MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
The MAH shall submit the final results and study report for the active treatment phase of the ALTITUDE study when available	31 July 2012
The MAH shall submit an updated risk management plan (RMP) that adequately describes all the safety concerns, the pharmacovigilance activities and the interventions designed to identify, characterise, prevent or minimise the risks.	Within a month following the Commission Decision

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

FOLDING BOX FOR UNIT PACK CONTAINING PVC/PCTFE BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Sprimeo HCT 150 mg/12.5 mg film-coated tablets
Aliskiren/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 150 mg aliskiren (as hemifumarate) and 12.5 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose and wheat starch.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 film-coated tablets
14 film-coated tablets
28 film-coated tablets
30 film-coated tablets
50 film-coated tablets
56 film-coated tablets
90 film-coated tablets
98 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the reach and sight 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
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/683/010	7 film-coated tablets
EU/1/11/683/011	14 film-coated tablets
EU/1/11/683/012	28 film-coated tablets
EU/1/11/683/013	30 film-coated tablets
EU/1/11/683/014	50 film-coated tablets
EU/1/11/683/015	56 film-coated tablets
EU/1/11/683/016	56 film-coated tablets (56x1; perforated unit dose blister)
EU/1/11/683/017	90 film-coated tablets
EU/1/11/683/018	98 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Sprimeo HCT 150 mg/12.5 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

FOLDING BOX FOR UNIT PACK CONTAINING PA/ALU/PVC BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Sprimeo HCT 150 mg/12.5 mg film-coated tablets
Aliskiren/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 150 mg aliskiren (as hemifumarate) and 12.5 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose and wheat starch.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 film-coated tablets
14 film-coated tablets
28 film-coated tablets
30 film-coated tablets
50 film-coated tablets
56 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the reach and sight 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
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/683/001	7 film-coated tablets
EU/1/11/683/002	14 film-coated tablets
EU/1/11/683/003	28 film-coated tablets
EU/1/11/683/004	30 film-coated tablets
EU/1/11/683/005	50 film-coated tablets
EU/1/11/683/006	56 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Sprimeo HCT 150 mg/12.5 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS (PVC/PCTFE OR PA/ALU/PVC)
BLISTER (CALENDAR) (PVC/PCTFE OR PA/ALU/PVC)

1. NAME OF THE MEDICINAL PRODUCT

Sprimeo HCT 150 mg/12.5 mg film-coated tablets
Aliskiren/hydrochlorothiazide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACKS (WITHOUT BLUE BOX) CONTAINING PVC/PCTFE BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Sprimeo HCT 150 mg/12.5 mg film-coated tablets
Aliskiren/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 150 mg aliskiren (as hemifumarate) and 12.5 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose and wheat starch.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
Component of a multipack comprising 20 packs, each containing 14 tablets.
49 film-coated tablets
Component of a multipack comprising 2 packs, each containing 49 tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the reach and sight 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
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/683/020	280 film-coated tablets (20x14)
EU/1/11/683/019	98 film-coated tablets (2x49; perforated unit dose blister)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Sprimeo HCT 150 mg/12.5 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACKS (WITHOUT BLUE BOX) CONTAINING PA/ALU/PVC BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Sprimeo HCT 150 mg/12.5 mg film-coated tablets
Aliskiren/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 150 mg aliskiren (as hemifumarate) and 12.5 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose and wheat starch.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
Component of a multipack comprising 20 packs, each containing 14 tablets.
30 film-coated tablets
Component of a multipack comprising 3 packs, each containing 30 tablets.
49 film-coated tablets
Component of a multipack comprising 2 packs, each containing 49 tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the reach and sight 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
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/683/009	280 film-coated tablets (20x14)
EU/1/11/683/007	90 film-coated tablets (3x30)
EU/1/11/683/011	98 film-coated tablets (2x49)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Sprimeo HCT 150 mg/12.5 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACKS (INCLUDING BLUE BOX) CONTAINING PVC/PCTFE BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Sprimeo HCT 150 mg/12.5 mg film-coated tablets
Aliskiren/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 150 mg aliskiren (as hemifumarate) and 12.5 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose and wheat starch.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

98 film-coated tablets
Multipack comprising 2 packs, each containing 49 tablets.
280 film-coated tablets
Multipack comprising 20 packs, each containing 14 tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the reach and sight 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
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/683/019	98 film-coated tablets (2x49; perforated unit dose blister)
EU/1/11/683/020	280 film-coated tablets (20x14)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Sprimeo HCT 150 mg/12.5 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACKS (INCLUDING BLUE BOX) CONTAINING PA/ALU/PVC BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Sprimeo HCT 150 mg/12.5 mg film-coated tablets
Aliskiren/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 150 mg aliskiren (as hemifumarate) and 12.5 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose and wheat starch.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

98 film-coated tablets
Multipack comprising 2 packs, each containing 49 tablets.
280 film-coated tablets
Multipack comprising 20 packs, each containing 14 tablets.
90 film-coated tablets
Multipack comprising 3 packs, each containing 30 tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the reach and sight 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
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/683/008	98 film-coated tablets (2x49)
EU/1/11/683/009	280 film-coated tablets (20x14)
EU/1/11/683/007	90 film-coated tablets (3x30)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Sprimeo HCT 150 mg/12.5 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

FOLDING BOX FOR UNIT PACK CONTAINING PVC/PCTFE BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Sprimeo HCT 150 mg/25 mg film-coated tablets
Aliskiren/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 150 mg aliskiren (as hemifumarate) and 25 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose and wheat starch.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 film-coated tablets
14 film-coated tablets
28 film-coated tablets
30 film-coated tablets
50 film-coated tablets
56 film-coated tablets
90 film-coated tablets
98 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the reach and sight 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
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/683/030	7 film-coated tablets
EU/1/11/683/031	14 film-coated tablets
EU/1/11/683/032	28 film-coated tablets
EU/1/11/683/033	30 film-coated tablets
EU/1/11/683/034	50 film-coated tablets
EU/1/11/683/035	56 film-coated tablets
EU/1/11/683/036	56 film-coated tablets (56x1; perforated unit dose blister)
EU/1/11/683/037	90 film-coated tablets
EU/1/11/683/038	98 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Sprimeo HCT 150 mg/25 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

FOLDING BOX FOR UNIT PACK CONTAINING PA/ALU/PVC BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Sprimeo HCT 150 mg/25 mg film-coated tablets
Aliskiren/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 150 mg aliskiren (as hemifumarate) and 25 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose and wheat starch.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 film-coated tablets
14 film-coated tablets
28 film-coated tablets
30 film-coated tablets
50 film-coated tablets
56 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the reach and sight 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
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/683/021	7 film-coated tablets
EU/1/11/683/022	14 film-coated tablets
EU/1/11/683/023	28 film-coated tablets
EU/1/11/683/024	30 film-coated tablets
EU/1/11/683/025	50 film-coated tablets
EU/1/11/683/026	56 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Sprimeo HCT 150 mg/25 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS (PVC/PCTFE OR PA/ALU/PVC)
BLISTER (CALENDAR) (PVC/PCTFE OR PA/ALU/PVC)

1. NAME OF THE MEDICINAL PRODUCT

Sprimeo HCT 150 mg/25 mg film-coated tablets
Aliskiren/hydrochlorothiazide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACKS (WITHOUT BLUE BOX) CONTAINING PVC/PCTFE BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Sprimeo HCT 150 mg/25 mg film-coated tablets
Aliskiren/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 150 mg aliskiren (as hemifumarate) and 25 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose and wheat starch.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
Component of a multipack comprising 20 packs, each containing 14 tablets.
49 film-coated tablets
Component of a multipack comprising 2 packs, each containing 49 tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the reach and sight 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
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/683/040	280 film-coated tablets (20x14)
EU/1/11/683/039	98 film-coated tablets (2x49; perforated unit dose blister)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Sprimeo HCT 150 mg/25 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACKS (WITHOUT BLUE BOX) CONTAINING PA/ALU/PVC BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Sprimeo HCT 150 mg/25 mg film-coated tablets
Aliskiren/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 150 mg aliskiren (as hemifumarate) and 25 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose and wheat starch.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
Component of a multipack comprising 20 packs, each containing 14 tablets.
30 film-coated tablets
Component of a multipack comprising 3 packs, each containing 30 tablets.
49 film-coated tablets
Component of a multipack comprising 2 packs, each containing 49 tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the reach and sight 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
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/683/029	280 film-coated tablets (20x14)
EU/1/11/683/027	90 film-coated tablets (3x30)
EU/1/11/683/028	98 film-coated tablets (2x49)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Sprimeo HCT 150 mg/25 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACKS (INCLUDING BLUE BOX) CONTAINING PVC/PCTFE BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Sprimeo HCT 150 mg/25 mg film-coated tablets
Aliskiren/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 150 mg aliskiren (as hemifumarate) and 25 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose and wheat starch.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

98 film-coated tablets
Multipack comprising 2 packs, each containing 49 tablets.
280 film-coated tablets
Multipack comprising 20 packs, each containing 14 tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the reach and sight 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
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/683/039	98 film-coated tablets (2x49; perforated unit dose blister)
EU/1/11/683/040	280 film-coated tablets (20x14)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Sprimeo HCT 150 mg/25 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACKS (INCLUDING BLUE BOX) CONTAINING PA/ALU/PVC BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Sprimeo HCT 150 mg/25 mg film-coated tablets
Aliskiren/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 150 mg aliskiren (as hemifumarate) and 25 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose and wheat starch.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

98 film-coated tablets
Multipack comprising 2 packs, each containing 49 tablets.
280 film-coated tablets
Multipack comprising 20 packs, each containing 14 tablets.
90 film-coated tablets
Multipack comprising 3 packs, each containing 30 tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the reach and sight 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
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/683/028	98 film-coated tablets (2x49)
EU/1/11/683/029	280 film-coated tablets (20x14)
EU/1/11/683/027	90 film-coated tablets (3x30)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Sprimeo HCT 150 mg/25 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

FOLDING BOX FOR UNIT PACK CONTAINING PVC/PCTFE BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Sprimeo HCT 300 mg/12.5 mg film-coated tablets
Aliskiren/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 300 mg aliskiren (as hemifumarate) and 12.5 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose and wheat starch.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 film-coated tablets
14 film-coated tablets
28 film-coated tablets
30 film-coated tablets
50 film-coated tablets
56 film-coated tablets
90 film-coated tablets
98 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the reach and sight 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
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/683/050	7 film-coated tablets
EU/1/11/683/051	14 film-coated tablets
EU/1/11/683/052	28 film-coated tablets
EU/1/11/683/053	30 film-coated tablets
EU/1/11/683/054	50 film-coated tablets
EU/1/11/683/055	56 film-coated tablets
EU/1/11/683/056	56 film-coated tablets (56x1; perforated unit dose blister)
EU/1/11/683/057	90 film-coated tablets
EU/1/11/683/058	98 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Sprimeo HCT 300 mg/12.5 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

FOLDING BOX FOR UNIT PACK CONTAINING PA/ALU/PVC BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Sprimeo HCT 300 mg/12.5 mg film-coated tablets
Aliskiren/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 300 mg aliskiren (as hemifumarate) and 12.5 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose and wheat starch.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 film-coated tablets
14 film-coated tablets
28 film-coated tablets
30 film-coated tablets
50 film-coated tablets
56 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the reach and sight 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
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/683/041	7 film-coated tablets
EU/1/11/683/042	14 film-coated tablets
EU/1/11/683/043	28 film-coated tablets
EU/1/11/683/044	30 film-coated tablets
EU/1/11/683/045	50 film-coated tablets
EU/1/11/683/046	56 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Sprimeo HCT 300 mg/12.5 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS (PVC/PCTFE OR PA/ALU/PVC)
BLISTER (CALENDAR) (PVC/PCTFE OR PA/ALU/PVC)

1. NAME OF THE MEDICINAL PRODUCT

Sprimeo HCT 300 mg/12.5 mg film-coated tablets
Aliskiren/hydrochlorothiazide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACKS (WITHOUT BLUE BOX) CONTAINING PVC/PCTFE BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Sprimeo HCT 300 mg/12.5 mg film-coated tablets
Aliskiren/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 300 mg aliskiren (as hemifumarate) and 12.5 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose and wheat starch.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
Component of a multipack comprising 20 packs, each containing 14 tablets.
49 film-coated tablets
Component of a multipack comprising 2 packs, each containing 49 tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the reach and sight 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
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/683/060	280 film-coated tablets (20x14)
EU/1/11/683/059	98 film-coated tablets (2x49; perforated unit dose blister)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Sprimeo HCT 300 mg/12.5 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACKS (WITHOUT BLUE BOX) CONTAINING PA/ALU/PVC BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Sprimeo HCT 300 mg/12.5 mg film-coated tablets
Aliskiren/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 300 mg aliskiren (as hemifumarate) and 12.5 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose and wheat starch.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
Component of a multipack comprising 20 packs, each containing 14 tablets.
30 film-coated tablets
Component of a multipack comprising 3 packs, each containing 30 tablets.
49 film-coated tablets
Component of a multipack comprising 2 packs, each containing 49 tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the reach and sight 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
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/683/049	280 film-coated tablets (20x14)
EU/1/11/683/047	90 film-coated tablets (3x30)
EU/1/11/683/048	98 film-coated tablets (2x49)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Sprimeo HCT 300 mg/12.5 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACKS (INCLUDING BLUE BOX) CONTAINING PVC/PCTFE BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Sprimeo HCT 300 mg/12.5 mg film-coated tablets
Aliskiren/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 300 mg aliskiren (as hemifumarate) and 12.5 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose and wheat starch.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

98 film-coated tablets
Multipack comprising 2 packs, each containing 49 tablets.
280 film-coated tablets
Multipack comprising 20 packs, each containing 14 tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the reach and sight 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
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/683/059	98 film-coated tablets (2x49; perforated unit dose blister)
EU/1/11/683/060	280 film-coated tablets (20x14)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Sprimeo HCT 300 mg/12.5 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACKS (INCLUDING BLUE BOX) CONTAINING PA/ALU/PVC BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Sprimeo HCT 300 mg/12.5 mg film-coated tablets
Aliskiren/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 300 mg aliskiren (as hemifumarate) and 12.5 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose and wheat starch.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

98 film-coated tablets
Multipack comprising 2 packs, each containing 49 tablets.
280 film-coated tablets
Multipack comprising 20 packs, each containing 14 tablets.
90 film-coated tablets
Multipack comprising 3 packs, each containing 30 tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the reach and sight 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
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/683/048	98 film-coated tablets (2x49)
EU/1/11/683/049	280 film-coated tablets (20x14)
EU/1/11/683/047	90 film-coated tablets (3x30)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Sprimeo HCT 300 mg/12.5 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

FOLDING BOX FOR UNIT PACK CONTAINING PVC/PCTFE BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Sprimeo HCT 300 mg/25 mg film-coated tablets
Aliskiren/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 300 mg aliskiren (as hemifumarate) and 25 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose and wheat starch.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 film-coated tablets
14 film-coated tablets
28 film-coated tablets
30 film-coated tablets
50 film-coated tablets
56 film-coated tablets
90 film-coated tablets
98 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the reach and sight 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
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/683/070	7 film-coated tablets
EU/1/11/683/071	14 film-coated tablets
EU/1/11/683/072	28 film-coated tablets
EU/1/11/683/073	30 film-coated tablets
EU/1/11/683/074	50 film-coated tablets
EU/1/11/683/075	56 film-coated tablets
EU/1/11/683/076	56 film-coated tablets (56x1; perforated unit dose blister)
EU/1/11/683/077	90 film-coated tablets
EU/1/11/683/078	98 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Sprimeo HCT 300 mg/25 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

FOLDING BOX FOR UNIT PACK CONTAINING PA/ALU/PVC BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Sprimeo HCT 300 mg/25 mg film-coated tablets
Aliskiren/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 300 mg aliskiren (as hemifumarate) and 25 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose and wheat starch.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 film-coated tablets
14 film-coated tablets
28 film-coated tablets
30 film-coated tablets
50 film-coated tablets
56 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the reach and sight 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
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/683/061	7 film-coated tablets
EU/1/11/683/062	14 film-coated tablets
EU/1/11/683/063	28 film-coated tablets
EU/1/11/683/064	30 film-coated tablets
EU/1/11/683/065	50 film-coated tablets
EU/1/11/683/066	56 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Sprimeo HCT 300 mg/25 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS (PVC/PCTFE OR PA/ALU/PVC)
BLISTER (CALENDAR) (PVC/PCTFE OR PA/ALU/PVC)

1. NAME OF THE MEDICINAL PRODUCT

Sprimeo HCT 300 mg/25 mg film-coated tablets
Aliskiren/hydrochlorothiazide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACKS (WITHOUT BLUE BOX) CONTAINING PVC/PCTFE BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Sprimeo HCT 300 mg/25 mg film-coated tablets
Aliskiren/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 300 mg aliskiren (as hemifumarate) and 25 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose and wheat starch.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
Component of a multipack comprising 20 packs, each containing 14 tablets.
49 film-coated tablets
Component of a multipack comprising 2 packs, each containing 49 tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the reach and sight 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
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/683/080	280 film-coated tablets (20x14)
EU/1/11/683/079	98 film-coated tablets (2x49; perforated unit dose blister)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Sprimeo HCT 300 mg/25 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACKS (WITHOUT BLUE BOX) CONTAINING PA/ALU/PVC BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Sprimeo HCT 300 mg/25 mg film-coated tablets
Aliskiren/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 300 mg aliskiren (as hemifumarate) and 25 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose and wheat starch.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
Component of a multipack comprising 20 packs, each containing 14 tablets.
30 film-coated tablets
Component of a multipack comprising 3 packs, each containing 30 tablets.
49 film-coated tablets
Component of a multipack comprising 2 packs, each containing 49 tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the reach and sight 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
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/683/069	280 film-coated tablets (20x14)
EU/1/11/683/067	90 film-coated tablets (3x30)
EU/1/11/683/068	98 film-coated tablets (2x49)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Sprimeo HCT 300 mg/25 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACKS (INCLUDING BLUE BOX) CONTAINING PVC/PCTFE BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Sprimeo HCT 300 mg/25 mg film-coated tablets
Aliskiren/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 300 mg aliskiren (as hemifumarate) and 25 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose and wheat starch.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

98 film-coated tablets
Multipack comprising 2 packs, each containing 49 tablets.
280 film-coated tablets
Multipack comprising 20 packs, each containing 14 tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the reach and sight 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
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/683/079	98 film-coated tablets (2x49; perforated unit dose blister)
EU/1/11/683/080	280 film-coated tablets (20x14)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Sprimeo HCT 300 mg/25 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACKS (INCLUDING BLUE BOX) CONTAINING PA/ALU/PVC BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Sprimeo HCT 300 mg/25 mg film-coated tablets
Aliskiren/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 300 mg aliskiren (as hemifumarate) and 25 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose and wheat starch.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

98 film-coated tablets
Multipack comprising 2 packs, each containing 49 tablets.
280 film-coated tablets
Multipack comprising 20 packs, each containing 14 tablets.
90 film-coated tablets
Multipack comprising 3 packs, each containing 30 tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the reach and sight 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
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/683/068	98 film-coated tablets (2x49)
EU/1/11/683/069	280 film-coated tablets (20x14)
EU/1/11/683/067	90 film-coated tablets (3x30)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Sprimeo HCT 300 mg/25 mg

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Sprimeo HCT 150 mg/12.5 mg film-coated tablets
Sprimeo HCT 150 mg/25 mg film-coated tablets
Sprimeo HCT 300 mg/12.5 mg film-coated tablets
Sprimeo HCT 300 mg/25 mg film-coated tablets
Aliskiren/hydrochlorothiazide

Read all of this leaflet carefully before you start taking this medicine.
- 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. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT SPRIMEO HCT IS AND WHAT IT IS USED FOR

Sprimeo HCT tablets contain two active substances, called aliskiren and hydrochlorothiazide. Both of these substances help to control high blood pressure (hypertension).

Aliskiren is a substance that belongs to a new group of medicines called renin inhibitors. These reduce the amount of angiotensin II the body can make. Angiotensin II causes blood vessels to tighten, which makes blood pressure higher. Lowering the amount of angiotensin II allows the blood vessels to relax; this lowers blood pressure.

Hydrochlorothiazide belongs to a group of medicines called thiazide diuretics. Hydrochlorothiazide increases urine output, which also lowers blood pressure.

High blood pressure increases the workload of the heart and arteries. If this continues for a long time, it can damage the blood vessels of the brain, heart and kidneys, and may result in a stroke, heart failure, heart attack or kidney failure. Lowering the blood pressure to a normal level reduces the risk of developing these disorders.

Sprimeo HCT is used to treat high blood pressure.

2. BEFORE YOU TAKE SPRIMEO HCT

Do not take Sprimeo HCT

- if you are allergic (hypersensitive) to aliskiren or hydrochlorothiazide, to sulphonamide-derived medicines (medicines used to treat chest or urinary infections) or to any of the other ingredients of Sprimeo HCT**.** If you think you may be allergic, do not take Sprimeo HCT and ask your doctor for advice.
- if you have experienced the following forms of angioedema (difficulties in breathing or swallowing, or swelling of the face, hands and feet, eyes, lips and/or tongue):
  - angioedema when taking aliskiren
  - hereditary angioedema
  - angioedema without any known cause.
- if you are more than 3 months pregnant. (It is also better to avoid Sprimeo HCT in early pregnancy – see Pregnancy section.)
- if you are between three and nine months pregnant.
- if you have serious liver or serious kidney problems.
- if you are unable to produce urine (anuria).
- if the level of potassium or sodium in your blood is too low despite treatment.
- if the level of calcium in your blood is too high despite treatment.
- if you have gout (uric acid crystals in the joints).
- if you are taking ciclosporin (a medicine used in transplantation to prevent organ rejection or for other conditions, e.g. rheumatoid arthritis or atopic dermatitis), itraconazole (a medicine used to treat fungal infections) or quinidine (a medicine used to correct heart rhythm).
- if you have diabetes mellitus or impaired kidney function and you are treated with either of the following classes of medicines used to treat high blood pressure:
  - an "angiotensin converting enzyme inhibitor" such as enalapril, lisinopril, ramipril etc.

  or
  - an "angiotensin 2 receptor blocker" such as valsartan, telmisartan, irbesartan etc.

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

Take special care with Sprimeo HCT

- if you have impaired kidney function, your doctor will carefully consider whether Sprimeo HCT is suitable for you and may wish to monitor you carefully.
- if you have had a kidney transplant.
- if you suffer from liver problems.
- if you suffer from heart problems.
- if you experience angioedema (difficulties in breathing, or swallowing, or swelling of the face, hands and feet, eyes, lips and/or tongue). If this happens, stop taking Sprimeo HCT and contact your doctor.
- if you have diabetes (high level of sugar in your blood).
- if you have a high level of cholesterol or triglycerides in your blood.
- if you suffer from a disease called lupus erythematosus (also called "lupus" or "SLE").
- if you suffer from allergy or asthma.
- if you are taking either of the following classes of medicines used to treat high blood pressure:
  - an "angiotensin converting enzyme inhibitor" such as enalapril, lisinopril, ramipril etc.

  or
  - an "angiotensin 2 receptor blocker" such as valsartan, telmisartan, irbesartan etc.
- if you are on a low-salt diet.
- if you have signs and symptoms such as abnormal thirst, dry mouth, general weakness, drowsiness, muscle pain or cramps, nausea, vomiting, or an abnormally fast heart beat which may indicate an excessive effect of hydrochlorothiazide (contained in Sprimeo HCT).
- if you experience skin reactions such as rash after sun exposure.
- if you experience a decrease in vision or eye pain. These could be symptoms of an increase of pressure in your eye and can happen within hours to weeks of taking Sprimeo HCT. This can lead to permanent vision impairment, if not treated.

Tell your doctor if any of the above applies to you.

You must tell your doctor if you think you are (or might become) pregnant. Sprimeo HCT is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see Pregnancy section).

The use of Sprimeo HCT in children and adolescents up to 18 years of age is not recommended.

Using other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

It is especially important to tell your doctor if you are using the following medicines:
- 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.
- medicines that may reduce the amount of potassium in your blood, such as diuretics (water tablets), corticosteroids, laxatives, carbenoxolone, amphotericin or penicillin G.
- 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 (carbamazepine).
- pain killers such as non-steroidal anti-inflammatory agents (NSAIDs), including selective cyclooxygenase-2 inhibitors (Cox-2 inhibitors).
- medicines to reduce blood pressure, including methyldopa.
- medicines to increase blood pressure, such as noradrenaline or adrenaline.
- digoxin or other digitalis glycosides (medicines used to treat heart problems).
- vitamin D and calcium salts.
- medicines for the treatment of diabetes (oral agents such as metformin or insulins).
- medicines that may increase blood sugar level, such as beta blockers and diazoxide.
- medicines for the treatment of gout, such as allopurinol.
- 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).
- amantadine (a medicine used to treat Parkinson's disease, also used to treat or prevent certain illnesses caused by viruses).
- cholestyramine, colestipol or other resins (substances used mainly to treat high levels of lipids in the blood).
- cytotoxic medicines (used to treat cancer), such as methotrexate or cyclophosphamide.
- muscle relaxants (medicines to relax the muscles which are used during operations).
- alcohol, sleeping pills and anaesthetics (medicines allowing patients to undergo surgery and other procedures).
- iodine contrast media (agents used for imaging examinations).
- arthritis medicines.

Your doctor may need to change your dose and/or take other precautions if you are taking one of the following medicines:
- furosemide, a medicine belonging to the type known as diuretics, or water tablets, which is used to increase the amount of urine you produce.
- some medicines used to treat infections, such as ketoconazole.
- verapamil, a medicine used to lower high blood pressure, to correct heart rhythm or to treat angina pectoris.

Taking Sprimeo HCT with food and drink
You should take Sprimeo HCT with a light meal once a day, preferably at the same time each day.
You should not take Sprimeo HCT together with grapefruit juice.

Pregnancy
You must tell your doctor if you think you are (or might become) pregnant. Your doctor will normally advise you to stop taking Sprimeo HCT before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of Sprimeo HCT. Sprimeo HCT is not recommended during 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. Sprimeo 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.

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

Driving and using machines
As with many other medicines used to treat high blood pressure, this medicine may make you feel dizzy. If you experience this symptom, do not drive or use tools or machines.

Important information about some of the ingredients of Sprimeo HCT
Sprimeo HCT contains lactose (milk sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

Sprimeo HCT contains wheat starch. It is suitable for people with coeliac disease. Patients with wheat allergy (different from coeliac disease) should not take this medicine.

3. HOW TO TAKE SPRIMEO HCT

Always take Sprimeo HCT exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The usual dose of Sprimeo HCT is one tablet a day. Swallow the tablet whole with some water. You should take Sprimeo HCT with a light meal once a day, preferably at the same time each day. You should not take Sprimeo HCT together with grapefruit juice. During your treatment, your doctor may adjust your dose depending on your blood pressure response.

Sprimeo HCT may have been prescribed to you because your previous treatment did not lower your blood pressure enough. If this is the case, your doctor will tell you how to switch from that treatment to Sprimeo HCT.

If you take more Sprimeo HCT than you should
If you have accidentally taken too many Sprimeo HCT tablets, talk to a doctor immediately. You may require medical attention.

If you forget to take Sprimeo 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.

Do not stop taking this medicine, even if you are feeling well (unless your doctor tells you to do so). People who have high blood pressure often do not notice any signs of the problem. Many may feel quite 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 further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Sprimeo HCT can cause side effects, although not everybody gets them.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist. You may need to stop Sprimeo HCT.

Side effects reported in clinical studies for patients treated with Sprimeo HCT were:
Common (affecting less than 1 in 10 patients):
- Diarrhoea

As for any combination of two active substances, side effects associated with each individual component cannot be excluded.
Aliskiren:
Common (affecting less than 1 in 10 patients):
- Diarrhoea
- Joint pain (arthralgia)
- High level of potassium in the blood
- Dizziness

Uncommon (affecting less than 1 in 100 patients):
- Skin rash (this may also be a sign of allergic reactions or angioedema – see "Rare" side effects below)
- Kidney problems including acute renal failure (severely decreased urine output)
- Swelling of hands, ankles or feet (peripheral oedema)
- Severe skin reactions (toxic epidermal necrolysis and/or oral mucosal reactions - red skin, blistering of the lips, eyes or mouth, skin peeling, fever)
- Low blood pressure

Rare (affecting less than 1 in 1,000 patients):
- Allergic reactions (hypersensitivity) and angioedema (the symptoms of which can include difficulties in breathing or swallowing, rash, itching, hives or swelling of the face, hands and feet, eyes, lips and/or tongue, dizziness)
- Increased level of creatinine in the blood

Hydrochlorothiazide:
Very common (affecting more than 1 in 10 patients):
- Low level of potassium in the blood
- Increase of lipids in the blood

Common (affecting less than 1 in 10 patients):
- 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

Rare (affecting less than 1 in 1,000 patients):
- Low level of blood platelets (sometimes with bleeding or bruising underneath the skin)
- High level of calcium in the blood
- High level of sugar in the blood
- Worsening of the diabetic metabolic state
- Sad mood (depression)
- Sleep disturbances
- Dizziness
- Headache
- Tingling or numbness
- Vision disorder
- Irregular heart beat
- Abdominal discomfort
- Constipation
- Diarrhoea
- Liver disorders which can occur together with yellow skin and eyes
- Increased sensitivity of skin to the sun
- Sugar in the urine

Very rare (affecting less than 1 in 10,000 patients):
- 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)
- Rash, itching, hives, difficulty breathing or swallowing, dizziness (hypersensitivity reactions)
- Confusion, tiredness, muscle twitching and spasm, rapid breathing (hypochloraemic alkalosis)
- Difficulty breathing with fever, coughing, wheezing, breathlessness (respiratory distress including pneumonitis and pulmonary oedema)
- Severe upper stomach pain (pancreatitis)
- 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):
- Weakness
- Bruising and frequent infections (aplastic anaemia)
- Decrease in vision or pain in your eyes due to high pressure (possible signs of acute-angle closure glaucoma)
- Severe skin disease that causes rash, red skin, blistering of the lips, eyes or mouth, skin peeling, fever (erythema multiforme)
- Muscle spasm
- Severely decreased urine output (possible signs of renal disorder or renal failure), weakness (asthenia)
- Fever

5. HOW TO STORE SPRIMEO HCT

Keep out of the reach and sight of children.
Do not use Sprimeo HCT after the expiry date which is stated on the carton. 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.

6. FURTHER INFORMATION

What Sprimeo HCT contains

- Each Sprimeo HCT 150 mg/12.5 mg film-coated tablet contains 150 mg aliskiren (as hemifumarate) and 12.5 mg hydrocholorothiazide. The other ingredients are: cellulose microcrystalline, crospovidone, lactose monohydrate, wheat starch, povidone, magnesium stearate, silica colloidal anhydrous, talc, hypromellose, macrogol, titanium dioxide (E171).
- Each Sprimeo HCT 150 mg/25 mg film-coated tablet contains 150 mg aliskiren (as hemifumarate) and 25 mg hydrocholorothiazide. The other ingredients are: cellulose microcrystalline, crospovidone, lactose monohydrate, wheat starch, povidone, magnesium stearate, silica colloidal anhydrous, talc, hypromellose, macrogol, titanium dioxide (E171), red iron oxide (E172), yellow iron oxide (E172).
- Each Sprimeo HCT 300 mg/12.5 mg film-coated tablet contains 300 mg aliskiren (as hemifumarate) and 12.5 mg hydrocholorothiazide. The other ingredients are: cellulose microcrystalline, crospovidone, lactose monohydrate, wheat starch, povidone, magnesium stearate, silica colloidal anhydrous, talc, hypromellose, macrogol, titanium dioxide (E171), red iron oxide (E172), black iron oxide (E172).
- Each Sprimeo HCT 300 mg/25 mg film-coated tablet contains 300 mg aliskiren (as hemifumarate) and 25 mg hydrocholorothiazide. The other ingredients are: cellulose microcrystalline, crospovidone, lactose monohydrate, wheat starch, povidone, magnesium stearate, silica colloidal anhydrous, talc, hypromellose, macrogol, titanium dioxide (E171), red iron oxide (E172), yellow iron oxide (E172).

What Sprimeo HCT looks like and contents of the pack

Sprimeo HCT 150 mg/12.5 mg film-coated tablets are white, oval film-coated tablets imprinted with "LCI" on one side and "NVR" on the other.
Sprimeo HCT 150 mg/25 mg film-coated tablets are pale yellow, oval film-coated tablets imprinted with "CLL" on one side and "NVR" on the other.
Sprimeo HCT 300 mg/12.5 mg film-coated tablets are violet white, oval film-coated tablets imprinted with "CVI" on one side and "NVR" on the other.
Sprimeo HCT 300 mg/25 mg film-coated tablets are light yellow, oval film-coated tablets imprinted with "CVV" on one side and "NVR" on the other.

Sprimeo HCT is available in packs containing 7, 14, 28, 30, 50, 56, 90,or 98 tablets.
Packs containing 90 (3x30), 98 (2x49) or 280 (20x14) tablets are multi-packs.

Not all pack sizes or strengths may be available in your country.

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