ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Sprimeo 150 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Light-pink, biconvex, round tablet, imprinted “IL” on one side and “NVR” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension.

4.2 Posology and method of administration

The recommended dose of Sprimeo is 150 mg once daily. In patients whose blood pressure is not adequately controlled, the dose may be increased to 300 mg once daily.

The antihypertensive effect is substantially present within two weeks (85-90%) after initiating therapy with 150 mg once daily.

Sprimeo may be used alone or in combination with other antihypertensive agents with the exception of use in combination with angiotensin converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB) in patients with diabetes mellitus or renal impairment (glomerular filtration rate (GFR) < 60 ml/min/1.73 m^2) (see sections 4.3, 4.4 and 5.1).

Sprimeo 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.

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). Sprimeo is not recommended in patients with severe renal impairment (GFR < 30 ml/min/1.73 m^2). Concomitant use of Sprimeo with ARBs or ACEIs is contraindicated in patients with renal impairment (GFR < 60 ml/min/1.73 m^2) (see section 4.3).

Hepatic impairment
No adjustment of the initial dose is required for patients with mild to severe hepatic impairment (see section 5.2).

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 (below 18 years)
Sprimeo 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 substance or to any of the excipients.

History of angioedema with aliskiren.

Hereditary or idiopathic angioedema.

Second and third trimesters of pregnancy (see section 4.6).

The concomitant use of aliskiren with ciclosporin and itraconazole, two highly potent 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

Aliskiren should be used with caution in patients with serious congestive heart failure (New York Heart Association [NYHA] functional class III-IV).

In the event of severe and persistent diarrhoea, Sprimeo therapy should be stopped.

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).

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 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 patients with marked volume- and/or salt-depletion (e.g. those receiving high doses of diuretics) symptomatic hypotension could occur after initiation of treatment with Sprimeo. This condition should be corrected prior to administration of Sprimeo, or the treatment should start under close medical supervision.

Renal impairment
In clinical studies Sprimeo has not been investigated in hypertensive patients with severe renal impairment (serum creatinine ≥ 150 µmol/l or 1.70 mg/dl in women and ≥ 177 µmol/l or 2.00 mg/dl in men and/or estimated GFR < 30 ml/min/1.73 m^2), history of dialysis, nephrotic syndrome or renovascular hypertension. Sprimeo is not recommended in patients with severe renal impairment (GFR < 30 ml/min/1.73 m^2).

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 (eg. due to blood loss, severe 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.

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.

Renal artery stenosis
No controlled clinical data are available on the use of Sprimeo 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.

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).

4.5 Interaction with other medicinal products and other forms of interaction

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 clinical pharmacokinetic studies include acenocoumarol, atenolol, celecoxib, pioglitazone, allopurinol, isosorbide-5-mononitrate and hydrochlorothiazide. No interactions have been identified.

Co-administration of aliskiren with either metformin (↓28%), amlodipine (↑29%) or cimetidine (↑19%) resulted in between 20% and 30% change in C_{max} or AUC of Sprimeo. When administered with atorvastatin, steady-state Sprimeo AUC and C_{max} increased by 50%. Co-administration of Sprimeo had no significant impact on atorvastatin, metformin or amlodipine pharmacokinetics. As a result no dose adjustment for Sprimeo or these co-administered medicinal products is necessary.

Digoxin and verapamil bioavailability may be slightly decreased by Sprimeo.

In experimental animals, it has been shown that P-gp is a major determinant of Sprimeo bioavailability. Inducers of P-gp (St. John's wort, rifampicin) might therefore decrease the bioavailability of Sprimeo.

CYP450 interactions
Aliskiren does not inhibit the CYP450 isoenzymes (CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A). Aliskiren does not induce CYP3A4. Therefore aliskiren is not expected to affect the systemic exposure of substances that inhibit, induce or are metabolised by these enzymes. Aliskiren is metabolised minimally by the cytochrome P450 enzymes. Hence, interactions due to inhibition or induction of CYP450 isoenzymes are not expected. However, CYP3A4 inhibitors often also affect P-gp. Increased aliskiren exposure during co-administration of CYP3A4 inhibitors that also inhibit P-gp can therefore be expected (see P-glycoprotein interactions below).

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 Sprimeo. 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).

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 that the effects be monitored when initiating and adjusting furosemide therapy to avoid possible underutilisation in clinical situations of volume overload.

Non-steroidal anti-inflammatory drugs (NSAIDs)
As with other agents acting on the renin-angiotensin system, NSAIDs may reduce the anti-hypertensive effect of aliskiren. In some patients with compromised renal function (dehydrated patients or elderly patients) aliskiren given concomitantly with NSAIDs may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore the combination of aliskiren with an NSAID requires caution, especially in elderly patients.

Medicinal products affecting serum potassium levels
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).

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.

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

Food intake
Meals with a high fat content have been shown to reduce the absorption of Sprimeo substantially.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data on the use of aliskiren in pregnant women. Sprimeo 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. As for any medicine that acts directly on the RAAS, Sprimeo 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). Healthcare professionals prescribing any agents acting on the RAAS should counsel women of childbearing potential about the potential risk of these agents during pregnancy. If pregnancy is detected during therapy, Sprimeo should be discontinued accordingly.

Breast-feeding
It is not known whether aliskiren is excreted in human milk. Sprimeo was secreted in the milk of lactating rats. Its use is therefore not recommended in women who are breast-feeding.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, when driving vehicles or operating machinery it must be borne in mind that dizziness or weariness may occasionally occur when taking any antihypertensive therapy. Sprimeo has negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Sprimeo has been evaluated for safety in more than 7,800 patients, including over 2,300 treated for over 6 months, and more than 1,200 for over 1 year. The incidence of adverse reactions showed no association with gender, age, body mass index, race or ethnicity. Treatment with Sprimeo resulted in an overall incidence of adverse reactions similar to placebo up to 300 mg. 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 adverse drug reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1

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.

Laboratory findings
In controlled clinical trials, clinically relevant changes in standard laboratory parameters were uncommonly associated with the administration of Sprimeo. In clinical studies in hypertensive patients, Sprimeo had no clinically important effects on total cholesterol, high density lipoprotein cholesterol (HDL-C), fasting triglycerides, fasting glucose or uric acid.

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.

4.9 Overdose

Limited data are available related to overdose in humans. The most likely manifestations of overdosage would be hypotension, related to the antihypertensive effect of aliskiren. 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, ATC code: C09XA02

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 (ACEI and angiotensin 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 differences in effect on PRA are not known at the present time.

Hypertension

In hypertensive patients, once-daily administration of Sprimeo 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, and was independent of age, gender, body mass index and ethnicity. Sprimeo has been studied in 1,864 patients aged 65 years or older, and in 426 patients aged 75 years or older.

Sprimeo monotherapy studies have shown blood pressure lowering effects comparable to other classes of antihypertensive agents including ACEI and ARB. Compared to a diuretic (hydrochlorothiazide - HCTZ), Sprimeo 300 mg lowered systolic/diastolic blood pressure by 17.0/12.3 mmHg, compared to 14.4/10.5 mmHg for HCTZ 25 mg after 12 weeks of treatment.

Combination therapy studies are available for Sprimeo added to the diuretic hydrochlorothiazide, the calcium channel blocker amlodipine and the beta blocker atenolol. These combinations were well tolerated. Sprimeo induced an additive blood-pressure-lowering effect when added to hydrochlorothiazide. In patients who did not adequately respond to 5 mg of the calcium channel blocker amlodipine, the addition of Sprimeo 150 mg had a blood-pressure-lowering effect similar to that obtained by increasing amlodipine dose to 10 mg, but had a lower incidence of oedema (aliskiren 150 mg/amlodipine 5 mg 2.1% vs. amlodipine 10 mg 11.2%).

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.

In obese hypertensive patients who did not adequately respond to HCTZ 25 mg, add-on treatment with Sprimeo 300 mg provided additional blood pressure reduction that was comparable to add-on treatment with irbesartan 300 mg or amlodipine 10 mg.

There has been no evidence of first-dose hypotension and no effect on pulse rate in patients treated in controlled clinical studies. Excessive hypotension was uncommonly (0.1%) seen in patients with uncomplicated hypertension treated with Sprimeo alone. Hypotension was also uncommon (<1%) during combination therapy with other antihypertensive agents. 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.

Beneficial effects of Sprimeo on mortality and cardiovascular morbidity and target organ damage are currently unknown.

Cardiac electrophysiology
No effect on QT interval was reported in a randomised, double-blind, placebo, and active-controlled study using standard and Holter electrocardiography.

5.2 Pharmacokinetic properties

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 (78%). 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/non-linearity
Exposure to aliskiren increased 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. At steady state the non-linearity may be more pronounced. Mechanisms responsible for deviation from linearity have not been identified. A possible mechanism is saturation of transporters at the absorption site or at the hepatobiliary clearance route.

Characteristics in patients
Aliskiren is an effective once-a-day antihypertensive treatment in adult patients, regardless of gender, age, body mass index and ethnicity.

The AUC is 50% higher in elderly (>65 years) than in young subjects. Gender, weight and ethnicity have no clinically relevant influence on aliskiren pharmacokinetics.

The pharmacokinetics of aliskiren were evaluated in patients with varying degrees of renal insufficiency. Relative AUC and C_{max} of aliskiren in subjects with renal impairment ranged between 0.8 to 2 times the levels in healthy subjects following single dose administration and at steady state. These observed changes, however, did not correlate with the severity of renal impairment. No adjustment of the initial dosage of Sprimeo is required in patients with mild to moderate renal impairment (see sections 4.2 and 4.4). Sprimeo is not recommended in patients with severe renal impairment (glomerular filtration rate (GFR) < 30 ml/min/1.73 m^2). Concomitant use of Sprimeo 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).

The pharmacokinetics of aliskiren were not significantly affected in patients with mild to severe liver disease. Consequently, no adjustment of the initial dose of aliskiren is required in patients with mild to severe hepatic impairment.

5.3 Preclinical safety data

Carcinogenic potential was assessed in a 2-year rat study and a 6-month transgenic mouse study. No carcinogenic potential was detected. One colonic adenoma and one caecal adenocarcinoma recorded in rats at the dose of 1,500 mg/kg/day were not statistically significant. Although aliskiren has known irritation potential, safety margins obtained in humans at the dose of 300 mg during a study in healthy volunteers were considered to be appropriate at 9-11-fold based on faecal concentrations or 6-fold based on mucosa concentrations in comparison with 250 mg/kg/day in the rat carcinogenicity study.

Aliskiren was devoid of any mutagenic potential in the *in vitro* and *in vivo* mutagenicity studies. The assays included *in vitro* assays in bacterial and mammalian cells and *in vivo* assessments in rats.

Reproductive toxicity studies with aliskiren did not reveal any evidence of embryofoetal toxicity or teratogenicity at doses up to 600 mg/kg/day in rats or 100 mg/kg/day in rabbits. Fertility, pre-natal development and post-natal development were unaffected in rats at doses up to 250 mg/kg/day. The doses in rats and rabbits provided systemic exposures of 1 to 4 and 5 times higher, respectively, than the maximum recommended human dose (300 mg).

Safety pharmacology studies 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Crospovidone
Magnesium stearate
Cellulose, microcrystalline
Povidone
Silica, colloidal anhydrous
Hypromellose
Macrogol
Talc
Iron oxide, black (E 172)
Iron oxide, red (E 172)
Titanium dioxide (E 171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

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

6.5 Nature and contents of container

PA/Alu/PVC – Alu blisters:
Packs containing 7, 14, 28, 30, 50, 56, 84, 90, 98 or 280 tablets.
Packs containing 84 (3x28), 98 (2x49) or 280 (20x14) tablets are multi-packs.

PVC/polychlorotrifluoroethylene (PCTFE) – Alu blisters:
Packs containing 14, 28, 30, 50, 56, 90, 98 or 280 tablets.
Packs containing 98 (2x49) or 280 (20x14) tablets are multi-packs.
Packs containing 56 and 98 (2x49) tablets are perforated unit-dose blisters.

Not all pack sizes 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/1/07/407/001-010
EU/1/07/407/021-030

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22.08.2007

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 300 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Light-red, biconvex, ovaloid tablet, imprinted “IU” on one side and “NVR” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension.

4.2 Posology and method of administration

The recommended dose of Sprimeo is 150 mg once daily. In patients whose blood pressure is not adequately controlled, the dose may be increased to 300 mg once daily.

The antihypertensive effect is substantially present within two weeks (85-90%) after initiating therapy with 150 mg once daily.

Sprimeo may be used alone or in combination with other antihypertensive agents with the exception of use in combination with angiotensin converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB) in patients with diabetes mellitus or renal impairment (glomerular filtration rate (GFR) < 60 ml/min/1.73 m^2) (see sections 4.3, 4.4 and 5.1).

Sprimeo 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.

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). Sprimeo is not recommended in patients with severe renal impairment (GFR < 30 ml/min/1.73 m^2). Concomitant use of Sprimeo with ARBs or ACEIs is contraindicated in patients with renal impairment (GFR < 60 ml/min/1.73 m^2) (see section 4.3).

Hepatic impairment
No adjustment of the initial dose is required for patients with mild to severe hepatic impairment (see section 5.2).

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 (below 18 years)
Sprimeo 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 substance or to any of the excipients.

History of angioedema with aliskiren.

Hereditary or idiopathic angioedema.

Second and third trimesters of pregnancy (see section 4.6).

The concomitant use of aliskiren with ciclosporin and itraconazole, two highly potent 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

Aliskiren should be used with caution in patients with serious congestive heart failure (New York Heart Association [NYHA] functional class III-IV).

In the event of severe and persistent diarrhoea, Sprimeo therapy should be stopped.

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).

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 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 patients with marked volume- and/or salt-depletion (e.g. those receiving high doses of diuretics) symptomatic hypotension could occur after initiation of treatment with Sprimeo. This condition should be corrected prior to administration of Sprimeo, or the treatment should start under close medical supervision.

Renal impairment
In clinical studies Sprimeo has not been investigated in hypertensive patients with severe renal impairment (serum creatinine ≥ 150 µmol/l or 1.70 mg/dl in women and ≥ 177 µmol/l or 2.00 mg/dl in men and/or estimated GFR < 30 ml/min/1.73 m^2), history of dialysis, nephrotic syndrome or renovascular hypertension. Sprimeo is not recommended in patients with severe renal impairment (GFR < 30 ml/min/1.73 m^2).

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 (eg. due to blood loss, severe 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.

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.

Renal artery stenosis
No controlled clinical data are available on the use of Sprimeo 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.

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).

4.5 Interaction with other medicinal products and other forms of interaction

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 clinical pharmacokinetic studies include acenocoumarol, atenolol, celecoxib, pioglitazone, allopurinol, isosorbide-5-mononitrate and hydrochlorothiazide. No interactions have been identified.

Co-administration of aliskiren with either metformin (↓28%), amlodipine (↑29%) or cimetidine (↑19%) resulted in between 20% and 30% change in C_{max} or AUC of Sprimeo. When administered with atorvastatin, steady-state Sprimeo AUC and C_{max} increased by 50%. Co-administration of Sprimeo had no significant impact on atorvastatin, metformin or amlodipine pharmacokinetics. As a result no dose adjustment for Sprimeo or these co-administered medicinal products is necessary.

Digoxin and verapamil bioavailability may be slightly decreased by Sprimeo.

In experimental animals, it has been shown that P-gp is a major determinant of Sprimeo bioavailability. Inducers of P-gp (St. John's wort, rifampicin) might therefore decrease the bioavailability of Sprimeo.

CYP450 interactions
Aliskiren does not inhibit the CYP450 isoenzymes (CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A). Aliskiren does not induce CYP3A4. Therefore aliskiren is not expected to affect the systemic exposure of substances that inhibit, induce or are metabolised by these enzymes. Aliskiren is metabolised minimally by the cytochrome P450 enzymes. Hence, interactions due to inhibition or induction of CYP450 isoenzymes are not expected. However, CYP3A4 inhibitors often also affect P-gp. Increased aliskiren exposure during co-administration of CYP3A4 inhibitors that also inhibit P-gp can therefore be expected (see P-glycoprotein interactions below).

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 Sprimeo. 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).

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 that the effects be monitored when initiating and adjusting furosemide therapy to avoid possible underutilisation in clinical situations of volume overload.

Non-steroidal anti-inflammatory drugs (NSAIDs)
As with other agents acting on the renin-angiotensin system, NSAIDs may reduce the anti-hypertensive effect of aliskiren. In some patients with compromised renal function (dehydrated patients or elderly patients) aliskiren given concomitantly with NSAIDs may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore the combination of aliskiren with an NSAID requires caution, especially in elderly patients.

Medicinal products affecting serum potassium levels
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).

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.

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

Food intake
Meals with a high fat content have been shown to reduce the absorption of Sprimeo substantially.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data on the use of aliskiren in pregnant women. Sprimeo 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. As for any medicine that acts directly on the RAAS, Sprimeo 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). Healthcare professionals prescribing any agents acting on the RAAS should counsel women of childbearing potential about the potential risk of these agents during pregnancy. If pregnancy is detected during therapy, Sprimeo should be discontinued accordingly.

Breast-feeding
It is not known whether aliskiren is excreted in human milk. Sprimeo was secreted in the milk of lactating rats. Its use is therefore not recommended in women who are breast-feeding.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, when driving vehicles or operating machinery it must be borne in mind that dizziness or weariness may occasionally occur when taking any antihypertensive therapy. Sprimeo has negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Sprimeo has been evaluated for safety in more than 7,800 patients, including over 2,300 treated for over 6 months, and more than 1,200 for over 1 year. The incidence of adverse reactions showed no association with gender, age, body mass index, race or ethnicity. Treatment with Sprimeo resulted in an overall incidence of adverse reactions similar to placebo up to 300 mg. 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 adverse drug reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1

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.

Laboratory findings
In controlled clinical trials, clinically relevant changes in standard laboratory parameters were uncommonly associated with the administration of Sprimeo. In clinical studies in hypertensive patients, Sprimeo had no clinically important effects on total cholesterol, high density lipoprotein cholesterol (HDL-C), fasting triglycerides, fasting glucose or uric acid.

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.

4.9 Overdose

Limited data are available related to overdose in humans. The most likely manifestations of overdosage would be hypotension, related to the antihypertensive effect of aliskiren. 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, ATC code: C09XA02

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 (ACEI and angiotensin 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 differences in effect on PRA are not known at the present time.

Hypertension

In hypertensive patients, once-daily administration of Sprimeo 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, and was independent of age, gender, body mass index and ethnicity. Sprimeo has been studied in 1,864 patients aged 65 years or older, and in 426 patients aged 75 years or older.

Sprimeo monotherapy studies have shown blood pressure lowering effects comparable to other classes of antihypertensive agents including ACEI and ARB. Compared to a diuretic (hydrochlorothiazide - HCTZ), Sprimeo 300 mg lowered systolic/diastolic blood pressure by 17.0/12.3 mmHg, compared to 14.4/10.5 mmHg for HCTZ 25 mg after 12 weeks of treatment.

Combination therapy studies are available for Sprimeo added to the diuretic hydrochlorothiazide, the calcium channel blocker amlodipine and the beta blocker atenolol. These combinations were well tolerated. Sprimeo induced an additive blood-pressure-lowering effect when added to hydrochlorothiazide. In patients who did not adequately respond to 5 mg of the calcium channel blocker amlodipine, the addition of Sprimeo 150 mg had a blood-pressure-lowering effect similar to that obtained by increasing amlodipine dose to 10 mg, but had a lower incidence of oedema (aliskiren 150 mg/amlodipine 5 mg 2.1% vs. amlodipine 10 mg 11.2%).

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.

In obese hypertensive patients who did not adequately respond to HCTZ 25 mg, add-on treatment with Sprimeo 300 mg provided additional blood pressure reduction that was comparable to add-on treatment with irbesartan 300 mg or amlodipine 10 mg.

There has been no evidence of first-dose hypotension and no effect on pulse rate in patients treated in controlled clinical studies. Excessive hypotension was uncommonly (0.1%) seen in patients with uncomplicated hypertension treated with Sprimeo alone. Hypotension was also uncommon (<1%) during combination therapy with other antihypertensive agents. 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.

Beneficial effects of Sprimeo on mortality and cardiovascular morbidity and target organ damage are currently unknown.

Cardiac electrophysiology
No effect on QT interval was reported in a randomised, double-blind, placebo, and active-controlled study using standard and Holter electrocardiography.

5.2 Pharmacokinetic properties

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 (78%). 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/non-linearity
Exposure to aliskiren increased 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. At steady state the non-linearity may be more pronounced. Mechanisms responsible for deviation from linearity have not been identified. A possible mechanism is saturation of transporters at the absorption site or at the hepatobiliary clearance route.

Characteristics in patients
Aliskiren is an effective once-a-day antihypertensive treatment in adult patients, regardless of gender, age, body mass index and ethnicity.

The AUC is 50% higher in elderly (>65 years) than in young subjects. Gender, weight and ethnicity have no clinically relevant influence on aliskiren pharmacokinetics.

The pharmacokinetics of aliskiren were evaluated in patients with varying degrees of renal insufficiency. Relative AUC and C_{max} of aliskiren in subjects with renal impairment ranged between 0.8 to 2 times the levels in healthy subjects following single dose administration and at steady state. These observed changes, however, did not correlate with the severity of renal impairment. No adjustment of the initial dosage of Sprimeo is required in patients with mild to moderate renal impairment (see sections 4.2 and 4.4). Sprimeo is not recommended in patients with severe renal impairment (glomerular filtration rate (GFR) < 30 ml/min/1.73 m^2). Concomitant use of Sprimeo 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).

The pharmacokinetics of aliskiren were not significantly affected in patients with mild to severe liver disease. Consequently, no adjustment of the initial dose of aliskiren is required in patients with mild to severe hepatic impairment.

5.3 Preclinical safety data

Carcinogenic potential was assessed in a 2-year rat study and a 6-month transgenic mouse study. No carcinogenic potential was detected. One colonic adenoma and one caecal adenocarcinoma recorded in rats at the dose of 1,500 mg/kg/day were not statistically significant. Although aliskiren has known irritation potential, safety margins obtained in humans at the dose of 300 mg during a study in healthy volunteers were considered to be appropriate at 9-11-fold based on faecal concentrations or 6-fold based on mucosa concentrations in comparison with 250 mg/kg/day in the rat carcinogenicity study.

Aliskiren was devoid of any mutagenic potential in the *in vitro* and *in vivo* mutagenicity studies. The assays included *in vitro* assays in bacterial and mammalian cells and *in vivo* assessments in rats.

Reproductive toxicity studies with aliskiren did not reveal any evidence of embryofoetal toxicity or teratogenicity at doses up to 600 mg/kg/day in rats or 100 mg/kg/day in rabbits. Fertility, pre-natal development and post-natal development were unaffected in rats at doses up to 250 mg/kg/day. The doses in rats and rabbits provided systemic exposures of 1 to 4 and 5 times higher, respectively, than the maximum recommended human dose (300 mg).

Safety pharmacology studies 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Crospovidone
Magnesium stearate
Cellulose, microcrystalline
Povidone
Silica, colloidal anhydrous
Hypromellose
Macrogol
Talc
Iron oxide, black (E 172)
Iron oxide, red (E 172)
Titanium dioxide (E 171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

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

6.5 Nature and contents of container

PA/Alu/PVC – Alu blisters:
Packs containing 7, 14, 28, 30, 50, 56, 84, 90, 98 or 280 tablets.
Packs containing 84 (3x28), 90 (3x30), 98 (2x49) or 280 (20x14) tablets are multi-packs.

PVC/polychlorotrifluoroethylene (PCTFE) – Alu blisters:
Packs containing 14, 28, 30, 50, 56, 90, 98 or 280 tablets.
Packs containing 98 (2x49) or 280 (20x14) tablets are multi-packs.
Packs containing 56 and 98 (2x49) tablets are perforated unit-dose blisters.

Not all pack sizes 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/1/07/407/011-020
EU/1/07/407/031-040

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22.08.2007

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
I-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 PA/ALU/PVC BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Sprimeo 150 mg film-coated tablets
Aliskiren

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

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

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/1/07/407/001	7 film-coated tablets
EU/1/07/407/002	14 film-coated tablets
EU/1/07/407/003	28 film-coated tablets
EU/1/07/407/004	30 film-coated tablets
EU/1/07/407/005	50 film-coated tablets
EU/1/07/407/006	56 film-coated tablets
EU/1/07/407/008	90 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 150 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

FOLDING BOX FOR UNIT PACK CONTAINING PCTFE/PVC BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Sprimeo 150 mg film-coated tablets
Aliskiren

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

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/1/07/407/021	14 film-coated tablets
EU/1/07/407/022	28 film-coated tablets
EU/1/07/407/023	30 film-coated tablets
EU/1/07/407/024	50 film-coated tablets
EU/1/07/407/025	56 film-coated tablets
EU/1/07/407/026	56 film-coated tablets (perforated unit-dose blister)
EU/1/07/407/027	90 film-coated tablets
EU/1/07/407/028	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 150 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER
BLISTER (CALENDAR)

1. NAME OF THE MEDICINAL PRODUCT

Sprimeo 150 mg film-coated tablets
Aliskiren

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 PA/ALU/PVC BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Sprimeo 150 mg film-coated tablets
Aliskiren

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
Component of a multipack comprising 20 packs, each containing 14 tablets.
28 film-coated tablets
Component of a multipack comprising 3 packs, each containing 28 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/1/07/407/007	84 film-coated tablets (3x28)
EU/1/07/407/009	98 film-coated tablets (2x49)
EU/1/07/407/010	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 150 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 150 mg film-coated tablets
Aliskiren

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

84 film-coated tablets
Multipack comprising 3 packs, each containing 28 tablets.
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/1/07/407/007	84 film-coated tablets (3x28)
EU/1/07/407/009	98 film-coated tablets (2x49)
EU/1/07/407/010	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 150 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

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

1. NAME OF THE MEDICINAL PRODUCT

Sprimeo 150 mg film-coated tablets
Aliskiren

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

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/1/07/407/029	98 film-coated tablets (2x49) (perforated unit-dose blister)
EU/1/07/407/030	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 150 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

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

1. NAME OF THE MEDICINAL PRODUCT

Sprimeo 150 mg film-coated tablets
Aliskiren

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

280 film-coated tablets
Multipack comprising 20 packs, each containing 14 tablets.
98 film-coated tablets
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/1/07/407/029	98 film-coated tablets (2x49) (perforated unit-dose blister)
EU/1/07/407/030	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 150 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 300 mg film-coated tablets
Aliskiren

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

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/1/07/407/011	7 film-coated tablets
EU/1/07/407/012	14 film-coated tablets
EU/1/07/407/013	28 film-coated tablets
EU/1/07/407/014	30 film-coated tablets
EU/1/07/407/015	50 film-coated tablets
EU/1/07/407/016	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 300 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

FOLDING BOX FOR UNIT PACK CONTAINING PCTFE/PVC BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Sprimeo 300 mg film-coated tablets
Aliskiren

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

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/1/07/407/031	14 film-coated tablets
EU/1/07/407/032	28 film-coated tablets
EU/1/07/407/033	30 film-coated tablets
EU/1/07/407/034	50 film-coated tablets
EU/1/07/407/035	56 film-coated tablets
EU/1/07/407/036	56 film-coated tablets (perforated unit-dose blister)
EU/1/07/407/037	90 film-coated tablets
EU/1/07/407/038	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 300 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER
BLISTER (CALENDAR)

1. NAME OF THE MEDICINAL PRODUCT

Sprimeo 300 mg film-coated tablets
Aliskiren

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 PA/ALU/PVC BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Sprimeo 300 mg film-coated tablets
Aliskiren

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
Component of a multipack comprising 20 packs, each containing 14 tablets.
28 film-coated tablets
Component of a multipack comprising 3 packs, each containing 28 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/1/07/407/017	84 film-coated tablets (3x28)
EU/1/07/407/018	90 film-coated tablets (3x30)
EU/1/07/407/019	98 film-coated tablets (2x49)
EU/1/07/407/020	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 300 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 300 mg film-coated tablets
Aliskiren

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

84 film-coated tablets
Multipack comprising 3 packs, each containing 28 tablets.
90 film-coated tablets
Multipack comprising 3 packs, each containing 30 tablets.
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/1/07/407/017	84 film-coated tablets (3x28)
EU/1/07/407/018	90 film-coated tablets (3x30)
EU/1/07/407/019	98 film-coated tablets (2x49)
EU/1/07/407/020	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 300 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

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

1. NAME OF THE MEDICINAL PRODUCT

Sprimeo 300 mg film-coated tablets
Aliskiren

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

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/1/07/407/039	98 film-coated tablets (2x49) (perforated unit-dose blister)
EU/1/07/407/040	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 300 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

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

1. NAME OF THE MEDICINAL PRODUCT

Sprimeo 300 mg film-coated tablets
Aliskiren

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

280 film-coated tablets
Multipack comprising 20 packs, each containing 14 tablets.
98 film-coated tablets
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/1/07/407/039	98 film-coated tablets (2x49) (perforated unit-dose blister)
EU/1/07/407/040	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 300 mg

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Sprimeo 150 mg film-coated tablets
Aliskiren

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 IS AND WHAT IT IS USED FOR

Sprimeo belongs to a new class of medicines called renin inhibitors. Sprimeo helps to lower high blood pressure. Renin inhibitors reduce the amount of angiotensin II the body can produce. Angiotensin II causes blood vessels to tighten, which increases the blood pressure. Reducing the amount of angiotensin II allows the blood vessels to relax, which lowers blood pressure.

High blood pressure increases the work load 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.

2. BEFORE YOU TAKE SPRIMEO

Do not take Sprimeo
- if you are allergic (hypersensitive) to aliskiren or any of the other ingredients of Sprimeo. If you think you may be allergic, 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.
- during the last 6 months of pregnancy or if you are breast-feeding, see section Pregnancy and breastfeeding.
- if you are taking ciclosporin (a medicine used in transplantation to prevent organ rejection or for other conditions, e.g. rheumathoid 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.

Take special care with Sprimeo
- if you are taking a diuretic (a type of medicine also known as "water" tablets which increases the amount of urine you produce).
- 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 have impaired kidney function, your doctor will carefully consider whether Sprimeo is suitable for you and may wish to monitor you carefully.
- 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 and contact your doctor.

If any of these apply to you, tell your doctor before you take Sprimeo.

The use of Sprimeo in children and adolescents is not recommended.
The usual dose of Sprimeo for patients aged 65 years or older is 150 mg.

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.

Your doctor may need to change your dose and/or to take other precautions if you are taking one of the following medicines:
- medicines that increase the amount of potassium in your blood. These include potassium-sparing diuretics, potassium supplements.
- furosemide, a medicine belonging to the type known as diuretics, or "water" tablets, which is used to increase the amount of urine you produce.
- one 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.
- ketoconazole, a medicine used to treat fungal infections.
- verapamil, a medicine used to lower high blood pressure, to correct heart rhythm or to treat angina pectoris.
- certain types of pain killers called non-steroidal anti-inflammatory medicines (NSAIDs).

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

Pregnancy and breast-feeding
Do not take Sprimeo if you are pregnant. It is important to talk to your doctor immediately if you think you may be pregnant or are planning to become pregnant. Do not breast-feed if you are taking Sprimeo.

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

Driving and using machines
You may feel dizzy and this can affect your ability to concentrate. Before you drive a vehicle, use machinery, or carry out other activities that require concentration, you should make sure you know how you react to the effects of Sprimeo.

3. HOW TO TAKE SPRIMEO

Always take Sprimeo exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

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.

The usual starting dose is one 150 mg tablet once daily.

Depending on how you respond to the treatment your doctor may prescribe a higher dose of one 300 mg tablet once daily. Your doctor may prescribe Sprimeo together with other medicines used to treat high blood pressure.

Method of administration
It is recommended that you take the tablets with some water. You should take Sprimeo with a light meal once a day, preferably at the same time each day. You should not take Sprimeo together with grapefruit juice.

If you take more Sprimeo than you should
If you have accidentally taken too many Sprimeo tablets, consult a doctor immediately. You may require medical attention.

If you forget to take Sprimeo
If you forget to take a dose of Sprimeo, take it as soon as you remember and then take the next dose at its usual time. However, 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 to make up for a forgotten dose.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Sprimeo 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.

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.

5. HOW TO STORE SPRIMEO

Keep out of the reach and sight of children.
Do not use Sprimeo after the expiry date which is stated on the carton and blister. 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 contains
- The active substance is aliskiren (as hemifumarate) 150 mg.
- The other ingredients are crospovidone, hypromellose, magnesium stearate, macrogol, microcrystalline cellulose, povidone, colloidal anhydrous silica, talc, titanium dioxide (E 171), black iron oxide (E 172), red iron oxide (E 172).

What Sprimeo looks like and contents of the pack
Sprimeo 150 mg film coated tablets are light-pink, biconvex round tablets, imprinted "IL" on one side and "NVR" on the other side.

Sprimeo is available in packs containing 7, 14, 28, 30, 50, 56, 84, 90, 98 or 280 tablets. Packs containing 84 (3x28), 98 (2x49) or 280 (20x14) tablets are multi-packs. Not all pack sizes may be available in your country.

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Manufacturer
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Italy

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This leaflet was last approved in

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

PACKAGE LEAFLET: INFORMATION FOR THE USER

Sprimeo 300 mg film-coated tablets
Aliskiren

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Method of administration
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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.

5. HOW TO STORE SPRIMEO

Keep out of the reach and sight of children.
Do not use Sprimeo after the expiry date which is stated on the carton and blister. 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 contains
- The active substance is aliskiren (as hemifumarate) 300 mg.
- The other ingredients are crospovidone, hypromellose, magnesium stearate, macrogol, microcrystalline cellulose, povidone, colloidal anhydrous silica, talc, titanium dioxide (E 171), black iron oxide (E 172), red iron oxide (E 172).

What Sprimeo looks like and contents of the pack
Sprimeo 300 mg film coated tablets are light-red, biconvex, ovaloid tablets, imprinted “IU” on one side and “NVR” on the other side.

Sprimeo is available in packs containing 7, 14, 28, 30, 50, 56, 84, 90, 98 or 280 tablets. Packs containing 84 (3x28), 90 (3x30), 98 (2x49) or 280 (20x14) tablets are multi-packs. Not all pack sizes may be available in your country.

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