ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

Medicinal product no longer authorised

1. NAME OF THE MEDICINAL PRODUCT

Tekturna 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 Tekturna 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.

Tekturna may be used alone or in combination with other antihypertensive agents (see sections 4.4 and 5.1).

Tekturna 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 Tekturna.

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

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)
No adjustment of the initial dose is required for elderly patients.

Paediatric patients (below 18 years)
Tekturna 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.

Medicinal product no longer authorised

History of angioedema with aliskiren.

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

The concomitant use of aliskiren with ciclosporin, a highly potent P-gp inhibitor, and other potent P-gp inhibitors (quinidine, verapamil), is contraindicated (see section 4.5).

4.4 Special warnings and precautions for use

Patients receiving other medicinal products inhibiting the renin-angiotensin system (RAS), and/or those with reduced kidney function and/or diabetes mellitus are at an increased risk of hyperkalaemia during aliskiren therapy.

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, Tekturna therapy should be stopped.

Angioedema
As with other agents acting on the renin-angiotensin system, angioedema has been reported in patients treated with aliskiren. If angioedema occurs, Tekturna 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 ensure patient 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 Tekturna. This condition should be corrected prior to administration of Tekturna, or the treatment should start under close medical supervision.

Renal impairment
In clinical studies Tekturna 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 glomerular filtration rate (GFR) < 30 ml/min), history of dialysis, nephrotic syndrome or renovascular hypertension. Caution should be exercised in hypertensive patients with severe renal impairment due to the lack of safety information for Tekturna.

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 or kidney disease. 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.

Renal artery stenosis
No controlled clinical data are available on the use of Tekturna 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 resulted in a 76% increase in aliskiren AUC but P-gp inhibitors such as ketoconazole are expected to increase tissue concentrations

Medicinal product no longer authorised

more than plasma concentrations. Therefore caution should be exercised when aliskiren is administered with moderate P-gp inhibitors such as ketoconazole (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Tekturna has no known clinically relevant interactions with medicinal products commonly used to treat hypertension or diabetes.

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

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

Digoxin bioavailability may be slightly decreased by Tekturna.

Preliminary data suggest that irbesartan may decrease Tekturna AUC and C_{max}.

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

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. Inducers of P-gp (St. John's wort, rifampicin) might therefore decrease the bioavailability of Tekturna. 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 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%.

Moderate P-gp inhibitors
Co-administration of ketoconazole (200 mg) with aliskiren (300 mg) resulted in an 80% increase in plasma levels of aliskiren (AUC and C_{max}). Preclinical studies indicate that aliskiren and ketoconazole co-administration enhances aliskiren gastrointestinal absorption and decreases biliary excretion. The change in plasma levels of aliskiren in the presence of ketoconazole 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

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trials. Yet, P-gp inhibitors are expected to increase tissue concentrations more than plasma concentrations. Therefore, caution should be exercised when aliskiren is administered with ketoconazole or other moderate pgp inhibitors (itraconazol, clarithromycin, telithromycin, erythromycin, amiodarone).

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. Therefore, concomitant use of aliskiren and P-gp potent inhibitors is contraindicated (see section 4.3).

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 under-utilisation 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.

Potassium and potassium-sparing diuretics
Based on experience with the use of other substances that affect the renin-angiotensin system, concomitant use of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other substances that may increase serum potassium levels (e.g. heparin) may lead to increases in serum potassium. If co-medication is considered necessary, caution is advisable.

Grapefruit juice
Due to the lack of data a potential interaction between grapefruit juice and aliskiren cannot be excluded. Grapefruit juice should not be taken together with Tekturna.

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

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

4.6 Pregnancy and lactation

Pregnancy
There are no data on the use of aliskiren in pregnant women. Tekturna was not teratogenic in rats or rabbits (see section 5.3). Other substances that act directly on the RAS have been associated with serious foetal malformations and neonatal death. As for any medicine that acts directly on the RAS, Tekturna 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 RAS should counsel women of childbearing potential about the potential risk of these agents during pregnancy. If pregnancy is detected during therapy, Tekturna should be discontinued accordingly.

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

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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. Tekturna has negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Tekturna 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 Tekturna 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 discontinuations of therapy. The most common adverse drug reaction is diarrhoea.

The incidence of cough was similar in placebo (0.6%) and Tekturna treated (0.9%) patients.

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), including isolated reports. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1

Gastrointestinal disorders	
Common:	Diarrhoea
Skin and subcutaneous tissue disorders	
Uncommon:	Rash
Rare:	Angioedema

Angioedema has occurred during treatment with Tekturna. In controlled clinical trials, angioedema occurred rarely during treatment with Tekturna with rates comparable to treatment with placebo or hydrochlorothiazide. Cases of angioedema have also been reported in post-marketing experience (frequency unknown). In the event of any signs suggesting an allergic reaction (in particular difficulties in breathing, or swallowing, or swelling of the face, extremities, eyes, lips and/or tongue) patients should discontinue treatment and contact the physician (see section 4.4).

Laboratory findings
In controlled clinical trials, clinically relevant changes in standard laboratory parameters were uncommonly associated with the administration of Tekturna. In clinical studies in hypertensive patients, Tekturna 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 angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers.

Serum potassium: Increases in serum potassium were minor and infrequent in patients with essential hypertension treated with Tekturna alone (0.9% compared to 0.6% with placebo). However, in one study where Tekturna was used in combination with an ACEI in a diabetic population, increases in serum potassium were more frequent (5.5%). Therefore as with any agent acting on the RAS system, routine monitoring of electrolytes and renal function is indicated in patients with diabetes mellitus, kidney disease, or heart failure.

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In post-marketing experience, renal dysfunction and cases of acute renal failure have been reported in patients at risk (see section 4.4).

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.

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 RAS 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 RAS (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 Tekturna 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 88% 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. Tekturna has been studied in 1,864 patients aged 65 years or older, and in 426 patients aged 75 years or older.

Tekturna 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), Tekturna 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. In diabetic hypertensive patients, Tekturna monotherapy was safe and effective.

Combination therapy studies are available for Tekturna added to the diuretic hydrochlorothiazide, the ACEI ramipril, the calcium channel blocker amlodipine, the angiotensin receptor antagonist valsartan, and the beta blocker atenolol. These combinations were well tolerated. Tekturna induced an additive blood-pressure-lowering effect when added to hydrochlorothiazide and to ramipril. In patients who did not adequately respond to 5 mg of the calcium channel blocker amlodipine, the addition of Tekturna 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%). Tekturna in combination with the angiotensin receptor antagonist valsartan showed an additive antihypertensive effect in the study specifically designed to investigate the effect of the combination therapy.

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

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provided additive blood pressure reductions when added to ramipril, while the combination of Tekturna and ramipril had a lower incidence of cough (1.8%) than ramipril (4.7%).

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 Tekturna 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 3-month study of 302 patients with mild stable heart failure, all of whom were receiving standard therapy for stable heart failure, addition of Tekturna 150 mg was well tolerated. B-type natriuretic peptide (BNP) levels were reduced by 25% in the Tekturna arm compared to placebo. However the clinical significance of this reduction is unknown.

In a 6-month study of 599 patients with hypertension, type 2 diabetes mellitus, and nephropathy, all of whom were receiving losartan 100 mg and optimised antihypertensive background therapy, addition of Tekturna 300 mg achieved a 20% reduction versus placebo in urinary albumin:creatinine ratio (UACR), i.e. from 58 mg/mmol to 46 mg/mmol. The proportion of patients who had UACR reduced at least 50% from baseline to endpoint was 24.7% and 12.5% for Tekturna and placebo, respectively. The clinical relevance of a reduction in UACR is not established in the absence of an effect on blood pressure. Tekturna did not affect the serum concentration of creatinine but was associated with an increased frequency (4.2% vs. 1.9% for placebo) of serum potassium concentration ≥6.0 mmol/l, although this was not statistically significant.

Beneficial effects of Tekturna 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

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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 Tekturna is required in patients with mild to severe renal impairment, however caution should be exercised in patients with severe renal impairment.

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

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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 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.

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/1/07/408/001-010

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22.08.2007

10. DATE OF REVISION OF THE TEXT

Medicinal product no longer authorised

1. NAME OF THE MEDICINAL PRODUCT

Tekturna 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 Tekturna 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.

Tekturna may be used alone or in combination with other antihypertensive agents (see sections 4.4 and 5.1).

Tekturna 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 Tekturna.

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

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)
No adjustment of the initial dose is required for elderly patients.

Paediatric patients (below 18 years)
Tekturna 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.

Medicinal product no longer authorised

History of angioedema with aliskiren.

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

The concomitant use of aliskiren with ciclosporin, a highly potent P-gp inhibitor, and other potent P-gp inhibitors (quinidine, verapamil), is contraindicated (see section 4.5).

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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, Tekturna therapy should be stopped.

Angioedema
As with other agents acting on the renin-angiotensin system, angioedema has been reported in patients treated with aliskiren. If angioedema occurs, Tekturna 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 ensure patient 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 Tekturna. This condition should be corrected prior to administration of Tekturna, or the treatment should start under close medical supervision.

Renal impairment
In clinical studies Tekturna 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 glomerular filtration rate (GFR) < 30 ml/min), history of dialysis, nephrotic syndrome or renovascular hypertension. Caution should be exercised in hypertensive patients with severe renal impairment due to the lack of safety information for Tekturna.

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 or kidney disease. 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.

Renal artery stenosis
No controlled clinical data are available on the use of Tekturna 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 resulted in a 76% increase in aliskiren AUC but P-gp inhibitors such as ketoconazole are expected to increase tissue concentrations

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

Digoxin bioavailability may be slightly decreased by Tekturna.

Preliminary data suggest that irbesartan may decrease Tekturna AUC and C_{max}.

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

<u>CYP450 interactions</u>
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).

<u>P-glycoprotein interactions</u>
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. Inducers of P-gp (St. John's wort, rifampicin) might therefore decrease the bioavailability of Tekturna. 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.

<u>P-gp substrates or weak inhibitors</u>
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%.

<u>Moderate P-gp inhibitors</u>
Co-administration of ketoconazole (200 mg) with aliskiren (300 mg) resulted in an 80% increase in plasma levels of aliskiren (AUC and C_{max}). Preclinical studies indicate that aliskiren and ketoconazole co-administration enhances aliskiren gastrointestinal absorption and decreases biliary excretion. The change in plasma levels of aliskiren in the presence of ketoconazole 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

Medicinal product no longer authorised

trials. Yet, P-gp inhibitors are expected to increase tissue concentrations more than plasma concentrations. Therefore, caution should be exercised when aliskiren is administered with ketoconazole or other moderate pgp inhibitors (itraconazol, clarithromycin, telithromycin, erythromycin, amiodarone).

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. Therefore, concomitant use of aliskiren and P-gp potent inhibitors is contraindicated (see section 4.3).

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 under-utilisation 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.

Potassium and potassium-sparing diuretics
Based on experience with the use of other substances that affect the renin-angiotensin system, concomitant use of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other substances that may increase serum potassium levels (e.g. heparin) may lead to increases in serum potassium. If co-medication is considered necessary, caution is advisable.

Grapefruit juice
Due to the lack of data a potential interaction between grapefruit juice and aliskiren cannot be excluded. Grapefruit juice should not be taken together with Tekturna.

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

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

4.6 Pregnancy and lactation

Pregnancy
There are no data on the use of aliskiren in pregnant women. Tekturna was not teratogenic in rats or rabbits (see section 5.3). Other substances that act directly on the RAS have been associated with serious foetal malformations and neonatal death. As for any medicine that acts directly on the RAS, Tekturna 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 RAS should counsel women of childbearing potential about the potential risk of these agents during pregnancy. If pregnancy is detected during therapy, Tekturna should be discontinued accordingly.

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

Medicinal product no longer authorised

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. Tekturna has negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Tekturna 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 Tekturna 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 discontinuations of therapy. The most common adverse drug reaction is diarrhoea.

The incidence of cough was similar in placebo (0.6%) and Tekturna treated (0.9%) patients.

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), including isolated reports. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1

Gastrointestinal disorders	
Common:	Diarrhoea
Skin and subcutaneous tissue disorders	
Uncommon:	Rash
Rare:	Angioedema

Angioedema has occurred during treatment with Tekturna. In controlled clinical trials, angioedema occurred rarely during treatment with Tekturna with rates comparable to treatment with placebo or hydrochlorothiazide. Cases of angioedema have also been reported in post-marketing experience (frequency unknown). In the event of any signs suggesting an allergic reaction (in particular difficulties in breathing, or swallowing, or swelling of the face, extremities, eyes, lips and/or tongue) patients should discontinue treatment and contact the physician (see section 4.4).

Laboratory findings
In controlled clinical trials, clinically relevant changes in standard laboratory parameters were uncommonly associated with the administration of Tekturna. In clinical studies in hypertensive patients, Tekturna 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 angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers.

Serum potassium: Increases in serum potassium were minor and infrequent in patients with essential hypertension treated with Tekturna alone (0.9% compared to 0.6% with placebo). However, in one study where Tekturna was used in combination with an ACEI in a diabetic population, increases in serum potassium were more frequent (5.5%). Therefore as with any agent acting on the RAS system, routine monitoring of electrolytes and renal function is indicated in patients with diabetes mellitus, kidney disease, or heart failure.

Medicinal product no longer authorised

In post-marketing experience, renal dysfunction and cases of acute renal failure have been reported in patients at risk (see section 4.4).

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.

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 RAS 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 RAS (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 Tekturna 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 88% 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. Tekturna has been studied in 1,864 patients aged 65 years or older, and in 426 patients aged 75 years or older.

Tekturna 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), Tekturna 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. In diabetic hypertensive patients, Tekturna monotherapy was safe and effective.

Combination therapy studies are available for Tekturna added to the diuretic hydrochlorothiazide, the ACEI ramipril, the calcium channel blocker amlodipine, the angiotensin receptor antagonist valsartan, and the beta blocker atenolol. These combinations were well tolerated. Tekturna induced an additive blood-pressure-lowering effect when added to hydrochlorothiazide and to ramipril. In patients who did not adequately respond to 5 mg of the calcium channel blocker amlodipine, the addition of Tekturna 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%). Tekturna in combination with the angiotensin receptor antagonist valsartan showed an additive antihypertensive effect in the study specifically designed to investigate the effect of the combination therapy.

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

Medicinal product no longer authorised

provided additive blood pressure reductions when added to ramipril, while the combination of Tekturna and ramipril had a lower incidence of cough (1.8%) than ramipril (4.7%).

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 Tekturna 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 3-month study of 302 patients with mild stable heart failure, all of whom were receiving standard therapy for stable heart failure, addition of Tekturna 150 mg was well tolerated. B-type natriuretic peptide (BNP) levels were reduced by 25% in the Tekturna arm compared to placebo. However the clinical significance of this reduction is unknown.

In a 6-month study of 599 patients with hypertension, type 2 diabetes mellitus, and nephropathy, all of whom were receiving losartan 100 mg and optimised antihypertensive background therapy, addition of Tekturna 300 mg achieved a 20% reduction versus placebo in urinary albumin:creatinine ratio (UACR), i.e. from 58 mg/mmol to 46 mg/mmol. The proportion of patients who had UACR reduced at least 50% from baseline to endpoint was 24.7% and 12.5% for Tekturna and placebo, respectively. The clinical relevance of a reduction in UACR is not established in the absence of an effect on blood pressure. Tekturna did not affect the serum concentration of creatinine but was associated with an increased frequency (4.2% vs. 1.9% for placebo) of serum potassium concentration ≥6.0 mmol/l, although this was not statistically significant.

Beneficial effects of Tekturna 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

Medicinal product no longer authorised

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 Tekturna is required in patients with mild to severe renal impairment, however caution should be exercised in patients with severe renal impairment.

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

Medicinal product no longer authorised

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 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.

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/1/07/408/011-020

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22.08.2007

10. DATE OF REVISION OF THE TEXT

Medicinal product no longer authorised

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

Medicinal product no longer authorised

A. MANUFACTURING AUTHORISATION HOLDER 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 OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription.

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

Not applicable.

- **OTHER CONDITIONS**

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance, as described in version 2 (dated 5 July 2006) presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

Risk Management Plan
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 30 May 2007 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the 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 EMEA.

Medicinal product no longer authorised

ANNEX III

LABELLING AND PACKAGE LEAFLET

Medicinal product no longer authorised

A. LABELLING

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

FOLDING BOX FOR UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Tekturna 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

Medicinal product no longer authorised

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/1/07/408/001	7 film-coated tablets
EU/1/07/408/002	14 film-coated tablets
EU/1/07/408/003	28 film-coated tablets
EU/1/07/408/004	30 film-coated tablets
EU/1/07/408/005	50 film-coated tablets
EU/1/07/408/006	56 film-coated tablets
EU/1/07/408/008	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

Tekturna 150 mg

Medicinal product no longer authorised

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER
BLISTER (CALENDAR)

1. NAME OF THE MEDICINAL PRODUCT

Tekturna 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

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACKS (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Tekturna 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.

Medicinal product no longer authorised

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/1/07/408/007	84 film-coated tablets (3x28)
EU/1/07/408/009	98 film-coated tablets (2x49)
EU/1/07/408/010	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

Tekturna 150 mg

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACKS (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Tekturna 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.

Medicinal product no longer authorised

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/1/07/408/007	84 film-coated tablets (3x28)
EU/1/07/408/009	98 film-coated tablets (2x49)
EU/1/07/408/010	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

Tekturna 150 mg

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

FOLDING BOX FOR UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Tekturna 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.

Medicinal product no longer authorised

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/1/07/408/011	7 film-coated tablets
EU/1/07/408/012	14 film-coated tablets
EU/1/07/408/013	28 film-coated tablets
EU/1/07/408/014	30 film-coated tablets
EU/1/07/408/015	50 film-coated tablets
EU/1/07/408/016	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

Tekturna 300 mg

Medicinal product no longer authorised

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER
BLISTER (CALENDAR)

1. NAME OF THE MEDICINAL PRODUCT

Tekturna 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

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACKS (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Tekturna 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

Medicinal product no longer authorised

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/1/07/408/017	84 film-coated tablets (3x28)
EU/1/07/408/018	90 film-coated tablets (3x30)
EU/1/07/408/019	98 film-coated tablets (2x49)
EU/1/07/408/020	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

Tekturna 300 mg

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACKS (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Tekturna 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

Medicinal product no longer authorised

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)

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EU/1/07/408/018	90 film-coated tablets (3x30)
EU/1/07/408/019	98 film-coated tablets (2x49)
EU/1/07/408/020	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

Tekturna 300 mg

Medicinal product no longer authorised

B. PACKAGE LEAFLET

Medicinal product no longer authorised

PACKAGE LEAFLET: INFORMATION FOR THE USER

Tekturna 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 TEKTURNA IS AND WHAT IT IS USED FOR

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

2. BEFORE YOU TAKE TEKTURNA

Do not take Tekturna
- if you are allergic (hypersensitive) to aliskiren or any of the other ingredients of Tekturna. If you think you may be allergic, ask your doctor for advice.
- if you have already experienced angioedema (difficulties in breathing, or swallowing, or swelling of the face, hands and feet, eyes, lips and/or tongue) when taking aliskiren.
- 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) or verapamil (a medicine used to lower blood pressure, to correct hearth rhythm or to treat angina pectoris) or quinidine (a medicine used to correct heart rhythm).

Take special care with Tekturna
- 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 have impaired kidney function.
- if you experience angioedema (difficulties in breathing, or swallowing, or swelling of the face, hands and feet, eyes, lips and/or tongue).

Medicinal product no longer authorised

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

The use of Tekturna in children and adolescents is not recommended.
There are no special dose recommendations for patients aged 65 years or older.

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.
- ketoconazole, a medicine used to treat fungal infections.
- certain types of pain killers called non-steroidal anti-inflammatory medicines (NSAIDs).

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

Pregnancy and breast-feeding
Do not take Tekturna 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 Tekturna.

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 Tekturna.

3. HOW TO TAKE TEKTURNA

Always take Tekturna 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 Tekturna 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 Tekturna with a light meal once a day, preferably at the same time each day. You should not take Tekturna together with grapefruit juice.

Medicinal product no longer authorised

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

If you forget to take Tekturna
If you forget to take a dose of Tekturna, 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, Tekturna can cause side effects, although not everybody gets them.

Common (affecting less than 1 in 10 patients): Diarrhoea.
Uncommon (affecting less than 1 in 100 patients): Skin rash.
Rare (affecting less than 1 in 1,000 patients): Angioedema (difficulties in breathing, or swallowing, or swelling of the face, hands and feet, eyes, lips and/or tongue).
Not known (frequency cannot be estimated from the available data): Kidney problems.

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.

5. HOW TO STORE TEKTURNA

Keep out of the reach and sight of children.
Do not use Tekturna 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 Tekturna 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 Tekturna looks like and contents of the pack
Tekturna 150 mg film coated tablets are light-pink, biconvex round tablets, imprinted "IL" on one side and "NVR" on the other side.

Tekturna 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.

Marketing Authorisation Holder
Novartis Europharm Limited
Wimblehurst Road
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United Kingdom

Medicinal product no longer authorised

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

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Novartis Pharmaceuticals UK Ltd.
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This leaflet was last approved in

Medicinal product no longer authorised

PACKAGE LEAFLET: INFORMATION FOR THE USER

Tekturna 300 mg film-coated tablets
Aliskiren

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- If you have any further questions, ask your doctor or pharmacist.
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- if you experience angioedema (difficulties in breathing, or swallowing, or swelling of the face, hands and feet, eyes, lips and/or tongue).

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- certain types of pain killers called non-steroidal anti-inflammatory medicines (NSAIDs).

Taking Tekturna with food and drink
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Pregnancy and breast-feeding
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The usual starting dose is one 150 mg tablet once daily.

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Method of administration
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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.

5. HOW TO STORE TEKTURNA

Keep out of the reach and sight of children.
Do not use Tekturna 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 Tekturna 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 Tekturna looks like and contents of the pack
Tekturna 300 mg film coated tablets are light-red, biconvex, ovaloid tablets, imprinted “IU” on one side and “NVR” on the other side.

Tekturna 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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