QUALITATIVE AND QUANTITATIVE COMPOSITION

Aprovasc® film coated tablet 150 mg/5 mg
Each tablet contains 150 mg irbesartan and 5 mg of amlodipine (7 mg of amlodipine besilate)
Aprovasc® film coated tablet 300 mg/10 mg
Each tablet contains 300 mg irbesartan and 10 mg of amlodipine (14 mg of amlodipine besilate)

List of excipient:
Cellulose microcrystalline PH 101, Cellulose microcrystalline PH 112, Croscarmellose sodium, Hypromellose, silicon dioxide, magnesium stearate, macrogol 400, titanium dioxide, purified water – trace.

Aprovasc® film coated tablet 300 mg/5 mg
Each tablet contains 300 mg irbesartan and 5 mg of amlodipine (7 mg of amlodipine besilate)

List of excipient:
Cellulose microcrystalline PH 101, Cellulose microcrystalline PH 112, Croscarmellose sodium, Hypromellose, silicon dioxide, magnesium stearate, macrogol 400, titanium dioxide, iron oxide yellow, macrogol 8000, purified water – trace.

Please note that not all strengths may be marketed

PHARMACEUTICAL FORM

Film coated tablet 150 mg/5 mg
White, oval shaped film coated tablets with '150/5' debossed on one side and plain on other side.
Film coated tablet 300 mg/5 mg
Yellow, oval shaped film coated tablets with '300/5' debossed on one side and plain on other side
Film coated tablet 300 mg/10 mg
White, oval shaped film coated tablets with SNAP TAB scoreline on one side and plain on other side. The tablet can be divided into equal halves

THERAPEUTIC INDICATIONS:

Treatment of essential hypertension.
Aprovasc® is indicated in the treatment of hypertension in adult patients in whom blood pressure is not adequately controlled on irbesartan or amlodipine monotherapy.

DOSAGE AND METHOD OF ADMINISTRATION:

The usual initial and maintenance dose of Aprovasc® is one tablet per day. Aprovasc® can be administered with or without food.
Aprovasc® should be administered in patients whose blood pressure is not adequately controlled on monotherapy with irbesartan or amlodipine or for continuation of therapy for patients receiving irbesartan and amlodipine as separate tablets. Dose should be determined on a case-by-case basis, based on patient response to therapy with the individual components and the desired antihypertensive response. The maximum recommended dose with Aprovasc® is 300 mg/10 mg per day.

Treatment should be adjusted based on blood pressure response.

Pediatric patients: The safety and efficacy of Aprovasc® has not been established in this population.

Elderly patients and patients with impaired renal function: In general, no dosage reduction is necessary in elderly patients or patients with impaired renal function (regardless of the degree of impairment).

Patients with impaired hepatic function: As the medicinal product contains amlodipine, Aprovasc® should be administered with caution in these patients (see Warnings).

Medicinal product for oral administration

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

The pharmacodynamic properties of each drug, Irbesartan and Amlodipine, provide an addition of antihypertensive effect when administered in combination compared to the effect of each drug administered separately. Both the AT1 receptor blocker and the calcium channel antagonist decrease blood pressure by reducing the peripheral resistance, but the calcium influx blockade and the vasoconstriction reduction by angiotensin II are complementary mechanisms.

Irbesartan:

Mechanism of action: Irbesartan is a specific antagonist of angiotensin II receptor (AT1 subtype). Angiotensin II is an important component of the renin-angiotensin system involved in the pathophysiology of hypertension and sodium homeostasis. Irbesartan does not require metabolic activation for its action.

Irbesartan blocks the potent vasoconstrictor and aldosterone-secreting effects of angiotensin II, by selective antagonism of angiotensin II receptors (AT1 subtype) localized in vascular smooth muscle cells and in the adrenal cortex. Irbesartan has no agonist activity in the AT1 receptor and has a much higher affinity (more than 8500- fold) for the AT1 receptor than for the AT2 receptor (receptor that has not shown to be associated with cardiovascular homeostasis).

Irbesartan does not inhibit the enzymes in the renin-angiotensin system, i.e., the angiotensin converting enzyme (ACE) , nor affects other hormone receptors or ion channels involved in the cardiovascular regulation of blood pressure and sodium homeostasis. The AT1 receptors blockade caused by Irbesartan interrupts the feedback loop within the renin-angiotensin system, resulting in increases in plasma levels of renin and angiotensin II. Aldosterone plasma concentrations decline following irbesartan administration, however, serum potassium levels are not significantly affected (mean increase of <0.1 mEq/L) at the recommended doses. Irbesartan has no notable effects on serum triglycerides, cholesterol or glucose concentrations. There is no effect on serum uric acid or urinary uric acid excretion.

Pharmacodynamic properties: The effect on the decrease in blood pressure by irbesartan is apparent after the first dose and becomes substantial within 1-2 weeks, with maximal effect occurs in 4-6 weeks. In long-term follow-up studies, the effect of irbesartan remained for more than one year.

A single daily dose up to 900 mg produced dose related drops in blood pressure. The 150-300 mg once a day dose decreases trough blood pressure in supine or sitting position (i.e., 24 hours after taking the dose), at an average of 8-13/5-8 mm Hg (systolic/diastolic) higher than those observed with placebo. The effects in trough are 60-70% of the corresponding peak diastolic and systolic responses. Optimal effects on blood pressure during the 24 hours are obtained with daily single dose.

Blood pressure decreases approximately to the same degree in both the standing position and the supine position. Orthostatic effects are not frequent, but as with ACE inhibitors, they can be expected in patients who have sodium- depletion and/or volume depletion.

The blood pressure lowering effects of irbesartan and thiazide-type diuretics are additive. In patients who are not adequately controlled by irbesartan alone, the addition of a low dose of hydrochlorothiazide (12.5 mg) to irbesartan once a day results in a greater reduction in blood pressure at trough of 7-10/3-6 mmHg (systolic/diastolic) compared to placebo.

Irbesartan effectiveness is not influenced by age or gender. As with other drugs that affect the renin-angiotensin

system, black patients have a markedly lower response to monotherapy with Irbesartan. When irbesartan is administered concomitantly with hydrochlorothiazide at low doses (12.5 mg daily), the antihypertensive response in black patients is similar to that of white patients. After the discontinuation of irbesartan, blood pressure gradually returns to the baseline. Rebound hypertension has not been observed

Amlodipine:

Mechanism of action: Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the entry of calcium ions and the transmembrane influx of these ions into both cardiac smooth muscle and vascular smooth muscle. The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on the vascular smooth muscle. The precise mechanism by which amlodipine alleviates angina symptoms has not been determined, however, amlodipine reduces the total ischemic burden through the following two actions:

1) Amlodipine dilates the peripheral arterioles and thus reduces the total peripheral resistance (after load) against which the heart works. Since the heart rate remains stable, this heart discharge reduces myocardial energy consumption and oxygen requirements;

2) Amlodipine mechanism of action probably involves also dilatation of the main arteries and coronary arterioles, both in ischemia and normal areas. This dilatation increases the oxygen supply to the myocardium in patients with coronary artery spasm (Prinzmetal's or variant angina).

Pharmacodynamic properties: In patients with hypertension, the administration of a daily dose produces significant reductions in blood pressure, in both standing and supine position for a period of 24 hours. Due to its slow onset of action, acute hypotension is not a characteristic of amlodipine administration.

In patients with angina, the administration of amlodipine once a day increases the total exercise time, the time to angina onset, and the time to 1 mm ST segment depression. In addition, it decreases both the frequency of angina attack and the consumption of nitroglycerin tablets.

Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids and is suitable for use in patients with asthma, diabetes, and gout.

Irbesartan / Amlodipine Combination:

The concurrent administration of irbesartan and amlodipine, either in a fixed dose combination tablet or the free dose combination, has no influence on the bioavailability of the individual components.

The three fixed-dose combinations of irbesartan and amlodipine (150 mg/10 mg, 300 mg/5 mg, and 300 mg/10 mg) are bioequivalent to free-dose combinations (150 mg/10 mg, 300 mg/5 mg, and 300 mg/10 mg) both in terms of rate and extent of absorption.

When administered separately or concomitantly at 300 mg and 10 mg dose levels, the time to mean peak plasma concentrations of irbesartan and amlodipine remain unchanged, i.e., 0.75-1 hour and 5 hours respectively after administration. Similarly, C_{max} and AUC are in the same range resulting in a relative bioavailability of 95% for irbesartan and 98% for amlodipine when administered in combination.

The mean half-life values for irbesartan and amlodipine, administered alone or in combination, are similar: 17.6 hours against 17.7 hours for irbesartan, and 58.5 hours against 52.1 hours for amlodipine. The elimination of irbesartan and amlodipine is unchanged when the drugs are administered alone or concomitantly.

Pediatric patients: No information available for the fixed dose combination.

CLINICAL EFFICACY/CLINICAL STUDIES

The clinical evidence for the efficacy of the irbesartan and amlodipine fixed-dose combination derives from two studies: I-ADD and I-COMBINE. Both were multicenter, prospective, randomized, open-label, parallel groups with blinded endpoint evaluation design. The studies were performed in patients with established, uncontrolled essential hypertension, [mean systolic blood pressure (SBP) ≥145 mmHg] after at least 4 weeks of treatment with irbesartan 150 mg (I-ADD) or amlodipine 5 mg (I-COMBINE).

Both studies consisted of three treatment periods, A, B, and C. During Period A, all patients received 5mg of amlodipine or 150 mg of Irbesartan, once daily, for 7 to 10 days. At the end of Period A, if the mean SBP of a patient was <135 mmHg, the patient was withdrawn from the corresponding study.

In the I-ADD study, patients (n=325) were randomized following Period A to receive either 150 mg of Irbesartan or the fixed- dose combination of 150 mg/5 mg of irbesartan/amlodipine once daily for 5 weeks (Period B).
In Week 5, doses were increased (forced titration) to 300 mg of Irbesartan or 300 mg/5 mg of the fixed-dose combination of irbesartan/amlodipine once daily and continued for 5 weeks.

In the I-COMBINE study, patients (n=290) were randomized following Period A to receive either 5mg of amlodipine or the fixed-dose combination of 150 mg/5 mg of irbesartan/amlodipine once daily for 5 weeks (Period B). At Week 5, doses were increased (forced titration) to 10mg of amlodipine or the fixed-dose combination of 150 mg/10 mg irbesartan/amlodipine once daily and continued for 5 weeks (Period C).

In the I-ADD study, the primary endpoint was the change in the SBP measured at home at Week 10.
In the I-COMBINE study, the primary endpoint was the change in the SBP measured at home at Week 5. Secondary endpoints were home diastolic blood pressure (DBP) and office blood pressure measurements (OBPM), as well as the percentage of controlled patients (mean SBP measured at home <135 mmHg) and patients with a response (mean SBP measured at home <135 mmHg and mean DBP measured at home <85 mmHg) at Week 10 for both studies.

The results of both studies demonstrated a significantly greater efficacy of the fixed-dose combination compared to amlodipine or irbesartan alone (see Tables 1 and 2).

Table 1: I-ADD Adjusted mean changes in blood pressure values from baseline assessment (mmHg)

	Fixed-dose combination (N=155)	Monotherapy with Irbesartan (N=165)		
BP in mmHg	Adjusted mean change from baseline assessment (SE)	Adjusted mean change from baseline assessment (SE)	Adjusted mean difference between groups (SE)	p-value
Week 5				
SBP at home (n=153/163)	-15.4 (0.8)	-5.6 (0.8)	-9.8 (1.1)	p<0.001
DBP at home (n= 153/163)	-7.4 (0.5)	-2.4 (0.5)	-5.0 (0.7)	p<0.001

SBP at doctor's office (n=154/164)	-14.7 (1.0)	-5.1 (1.0)	-9.6 (1.4)	p<0.001
DBP at doctor's office (n= 154/164)	-7.3 (0.7)	-2.4 (0.6)	-4.9 (0.9)	p<0.001
Week 10				
SBP at home * (n= 146/153)	-18.7 (0.8)	-9.9 (0.8)	-8.8 (1.1)	p<0.001
DBP at home (n= 146/153)	-8.6 (0.5)	-3.9 (0.5)	-4.7 (0.7)	p<0.001
SBP at doctor's office (n=149/162)	-17.9 (1.2)	-8.4 (1.1)	-9.5 (1.6)	p<0.001
DBP at doctor's office (n= 149/162)	-7.7 (0.7)	-3.5 (0.7)	-4.2 (1.0)	p<0.001
* Primary endpoint n=number of evaluable patients in the fixed-dose combination /number of evaluable patients in the monotherapy group				

Table 2 - I-Combine – Adjusted mean changes in blood pressure values from the baseline assessment (mmHg) – ITT Population

	Fixed-dose combination (N=144)	Amlodipine (N=143)		
BP in mmHg	Adjusted mean change from baseline assessment (SE)	Adjusted mean change from baseline assessment (SE)	Adjusted mean difference between groups (SE)	p-value
Week 5				
SBP at home (n= 141/139)*	-12.4 (0.7)	-6.3 (0.7)	-6.2 (1.0)	p<0.001
DBP at home (n= 141/139)	-5.6 (0.5)	-3.0 (0.5)	-2.6 (0.7)	p<0.001
SBP at doctor's office (n=143/143)	-10.8 (1.0)	-3.3 (1.0)	-7.4 (1.4)	p<0.001

DBP at doctor's office (n= 143/143)	-3.8 (0.6)	-1.2 (0.6)	-2.6 (0.9)	P=0.004
Week 10				
SBP at home (n=132/131)	-18.1 (0.7)	-13.5 (0.7)	-4.5 (1.0)	p<0.001
DBP at home (n= 132/131)	-9.4 (0.5)	-6.2 (0.5)	-3.2 (0.7)	p<0.001
SBP at doctor's office (n= 134/136)	-18.4 (1.1)	-12.4 (1.1)	-6.0 (1.6)	p<0.001
DBP at doctor's office (n= 134/136)	-8.7 (0.6)	-5.6 (0.6)	-3.1 (0.9)	p<0.001

* Primary endpoint

n=number of evaluable patients in the fixed-dose combination /number of evaluable patients in the monotherapy group

Pharmacokinetics properties

Irbesartan:

Irbesartan is an orally active agent and does not require biotransformation for its activity. After oral administration, irbesartan is rapidly and completely absorbed. Peak plasma concentrations occurs at 1.5-2 hours after oral administration. The absolute bioavailability of irbesartan administered orally is 60-80%. Food does not affect the bioavailability of irbesartan.

Irbesartan is approximately 96% protein-bound in plasma and has negligible binding to cellular components of blood. The distribution volume is 53-93 L/Kg.

In plasma, unchanged irbesartan accounts for 80-85% of the circulating radioactivity after oral or intravenous administration of Irbesartan C^{14}. Irbesartan is metabolized by the liver via glucuronide conjugation and oxidation. The main circulating metabolite is irbesartan glucuronide (approximately 6%). Irbesartan undergoes oxidation primarily by the cytochrome P450 isoenzyme CYP2C9; the CYP3A4 isoenzyme has a negligible effect. Irbesartan is not metabolized by most of the isoenzymes commonly involved in drug metabolism, nor induces or inhibits them substantially (i.e., CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2D6, or CYP2E1). Irbesartan does not induce or inhibit the CYP3A4 isoenzyme.

Irbesartan and its metabolites are excreted by both biliary and renal routes. About 20% of the administered radioactivity after a dose of Irbesartan C^{14}, orally or intravenously, is recovered in the urine and the rest in the feces. Less than 2% of the dose is excreted in the urine as unchanged irbesartan.

Irbesartan terminal elimination half-life ($t_{1/2}$) is 11-15 hours. The total body clearance of intravenously administered irbesartan is 157-176 mL/min, of which 3.0-3.5 mL/min is renal clearance. Irbesartan exhibits a linear pharmacokinetics over the therapeutic dose range. Steady-state plasma concentrations are reached within three days after the start of the once a day dosing regimen. Limited accumulation (<20%) is observed in plasma when the daily dose is repeated.

In hypertensive individuals, higher plasma concentrations (11-44%) of Irbesartan were observed in women than in men; However, after multiple doses, no differences were observed in either accumulation or elimination half-life between men and women. No gender-specific differences in clinical effect have been observed.

In elderly normotensive subjects (men and women) (65-80 years old) with clinically normal renal and hepatic function, AUC and peak plasma concentrations (C_{max}) of Irbesartan were approximately 20-50% higher than those observed in younger subjects (18-40 years old). Regardless of age, the elimination half-life is comparable.

No significant age-related differences in clinical effect have been observed.

In black and white normotensive subjects, irbesartan AUC in plasma and terminal elimination half-life ($t_{1/2}$) are approximately 20 to 25% higher in blacks than whites, Irbesartan peak plasma concentrations (C_{max}) were essentially equivalent.

In patients with renal impairment (regardless of degree) and in patients on hemodialysis, Irbesartan pharmacokinetics did not change significantly. Irbesartan is not removed by hemodialysis.

In patients with hepatic insufficiency due to mild to moderate cirrhosis, the pharmacokinetics of irbesartan was not significantly affected.

Amlodipine:
After oral administration of therapeutic doses, amlodipine is well absorbed, with peak blood levels between 6 to 12 hours after dose administration. Absolute bioavailability is estimated to be between 64 to 80%. The volume of distribution is approximately 21 L/kg. *In vitro* studies have shown approximately 97.5% circulating amlodipine is bound to plasma proteins. Absorption of amlodipine is not affected by food intake.

The plasma terminal elimination half-life is around 35 to 50 hours and is consistent with the dosage once a day. Amlodipine is extensively metabolized by the liver to inactive metabolites, with 10% of the parent compound and 60% of metabolites excreted in the urine.

Use in the elderly: The time to reach peak plasma concentrations of amlodipine is similar in elderly and young patients. Clearance of amlodipine tends to be reduced with resulting increases in the AUC and the elimination half-life in elderly patients.

The increases in the AUC and elimination half-life in patients with congestive heart failure were as expected in this age group.

Patients with liver failure: Very limited clinical data are available on the administration of amlodipine in patients with liver failure. Patients with liver failure have reduced amlodipine clearance, resulting in a longer half-life.

Irbesartan/Amlodipine combination:
The pharmacokinetics of both drugs appear to be linear in the range of doses administered together (i.e. between 150 mg and 300 mg for irbesartan, and between 5 mg and 10 mg for amlodipine).

CONTRAINDICATIONS:
Due to the presence of both irbesartan and amlodipine, Aprovasc® is contraindicated in:

- Hypersensitivity to irbesartan, amlodipine, dihydropyridines or to any formulation component.
- Shock (including cardiogenic shock).
- Obstruction of the left ventricular outflow tract (e.g. clinically significant aortic stenosis).
- Unstable angina (excluding Prinzmetal's angina).
- Haemodynamically unstable heart failure following an acute myocardial infarction.
- Severe hypotension.
- Pregnancy and lactation (see Warnings and Pregnancy and Lactation).

Do not co-administer APROVASC® with medications containing aliskiren in patients with diabetes or with moderate to severe renal impairment (Glomerular Filtration Rate (GFR) < 60 mL/min/1.73 m2).

Do not co-administer APROVASC® with angiotensin-converting enzyme inhibitors (ACEIs) in patients with diabetic nephropathy.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
***Special warnings*:**

Hypotension – Patients with volume depletion: Symptomatic hypotension may occur in patients with sodium/ volume depletion and in those under intensive treatment with diuretics and/or salt restriction, or in hemodialysis. The depletion of volume and/or sodium should be corrected before starting treatment with Aprovasc®.

Hypoglycaemia: Irbesartan may induce hypoglycaemia, particularly in diabetic patients. In patients treated with insulin or antidiabetics an appropriate blood glucose monitoring should be considered; a dose adjustment of insulin or antidiabetics may be required when indicated.

Fetal/neonatal morbidity and mortality: Although there is no experience with irbesartan in pregnant women, it has been reported that exposure to ACE inhibitors, administered to pregnant women during the second and third trimesters of pregnancy, may cause injuries and death to the fetus. Therefore, as any other drug acting directly on the renin-angiotensin-aldosterone system, Aprovasc® should not be administered during pregnancy. If pregnancy is detected during treatment, Aprovasc® should be discontinued as soon as possible.

Patients with heart failure: Patients with heart failure must be treated cautiously. In a long-term, placebo-controlled study (PRAISE-2) of amlodipine in patients with NYHA class III and IV heart failure of non-ischaemic origin, the use of amlodipine is associated with an increase in reports of pulmonary oedema despite no significant difference in the frequency of cases in which the heart failure worsened as compared to placebo (see Pharmacokinetics and Pharmacodynamics).

Hepatic impairment:
<u>For amlodipine</u>
As with other calcium antagonists, the half-life of amlodipine is prolonged and the AUC values are greater in patients with impaired liver function and dose recommendations have not been established for this group. Therefore, amlodipine must be initiated at the lowest possible dose range and should be used with caution, both on initial treatment and when increasing the dose in these patients. A slow dose adjustment and careful monitoring in patients with severe liver failure may be necessary.

Hypertensive crisis: The safety and efficacy of Aprovasc® in the treatment of hypertensive crisis has not been established.

General precautions:

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
The dual blockade of the renin-angiotensin-aldosterone system by combining Aprovasc® with angiotensin-converting enzyme inhibitors (ACEIs) or with aliskiren is not recommended since there is an increased risk of hypotension, hyperkalemia and decreased renal function compared to monotherapy.
If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.
The use of Aprovasc® in combination with aliskiren is contraindicated in patients with diabetes mellitus or renal failure (Glomerular Filtration Rate (GFR) <60 mL/min/1.73 m^2).
The use of Aprovasc® in combination with ACE-inhibitors is contraindicated in patients with diabetic nephropathy.
The use of Aprovasc® in patients with psoriasis or with a history of psoriasis should be weighed carefully as it may exacerbate psoriasis.

Renovascular hypertension: there is an increased risk of severe hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with medicinal products that affect the renin-angiotensin-aldosterone system. While this is not documented with Aprovasc, a similar effect should be anticipated with angiotensin II receptor antagonists.

Renal impairment and kidney transplantation: when Aprovasc is used in patients with impaired renal function, a periodic monitoring of potassium and creatinine serum levels is recommended. There is no experience regarding the administration of Aprovasc in patients with a recent kidney transplantation.

Hypertensive patients with type 2 diabetes and renal disease: the effects of irbesartan both on renal and cardiovascular events were not uniform across all subgroups, in an analysis carried out in the study with patients with advanced renal disease. In particular, they appeared less favourable in women and non-white subjects *(see Pharmacodynamic properties)*.

Hyperkalaemia: as with other medicinal products that affect the renin-angiotensin-aldosterone system, hyperkalaemia may occur during the treatment with Aprovasc, especially in the presence of renal impairment, overt proteinuria due to diabetic renal disease, and/or heart failure. Close monitoring of serum potassium in patients at risk is recommended *(see Interaction with other medicinal products and other forms of interaction).*

Primary aldosteronism: patients with primary aldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of Aprovasc is not recommended.

General
Changes in the renal function of susceptible individuals can be expected as a consequence of the inhibition of the renin-angiotensin-aldosterone system. In patients whose renal function depends on the activity of the renin-angiotensin-aldosterone system (hypertensive patients with renal artery stenosis in one or both kidneys, or patients with severe congestive heart failure), treatment with other drugs that affect this system has been associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death. The possibility of a similar effect occurring with the use of an angiotensin II receptor antagonist, including irbesartan, cannot be excluded.

Geriatric use: In elderly patients with volume depletion (including those on therapy with diuretics), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with angiotensin II receptor antagonists, can cause a deterioration of renal function, including a possible acute renal failure. These effects are usually reversible. Renal function should be monitored in patients receiving periodic treatment with irbesartan and NSAIDs. The antihypertensive effect of angiotensin II receptor antagonists can be attenuated by NSAIDs including selective COX-2 inhibitors. Among patients who received irbesartan in clinical studies, no overall differences were observed in terms of efficacy and safety in older patients (65 years or older) or in younger patients.

Pediatric use: Safety and efficacy in pediatric patients have not been established.

Lithium
The concomitant use of angiotensin II receptor blockers and calcium channel blockers may reduce renal lithium clearance and the increase of serum levels that may reach toxic levels. Hence, the combination of lithium and Aprovasc is not recommended.

Effects on ability to drive

For irbesartan: The effect of irbesartan on the ability to drive and use machines has not been investigated. Based on its pharmacodynamic properties, it is unlikely that irbesartan will have an effect on the ability to drive or operate machines. However, it should be taken into account that patients being treated for hypertension may occasionally experience dizziness or tiredness.

For amlodipine: Amlodipine may have a mild or moderate effect on the ability to drive and use machines. If

patients taking amlodipine experience dizziness, headache, fatigue or nausea, the reaction speed may be affected. Caution is advised especially when starting treatment.

FERTILITY, PREGNANCY AND LACTATION

Pregnancy*:* There are no adequate and well-controlled studies in pregnant women. Aprovasc® is contraindicated during pregnancy. Aprovasc® should not be used in women of childbearing potential unless effective contraceptive measures are being used. If pregnancy occurs during treatment with Aprovasc®, this should be discontinued as soon as possible (see Contraindications and Warnings).

Lactation*:* Aprovasc® is contraindicated during lactation (see Contraindications).

SIDE-EFFECTS AND ADVERSE REACTIONS:

Adverse events:

Since clinical studies are conducted under broadly variable conditions, the incidence of adverse reactions observed in drug clinical studies cannot be directly compared to clinical studies with other medications and may not reflect the rates observed in practice.

For irbesartan

Irbesartan safety has been evaluated in clinical studies with approximately 5000 subjects, including 1300 hypertensive patients treated for 6 months and more than 400 patients treated for 1 year or more. In general, adverse events in patients receiving irbesartan were mild and transient and were not related to the dose. The incidence of adverse events was not related to age, gender, or race.

In placebo-controlled clinical trials, including 1965 patients treated with irbesartan (usual treatment duration of 1 to 3 months), the discontinuation of treatment due to any clinical or laboratory adverse event was 3.3 percent for patients treated with Irbesartan and 4.5 percent for patients treated with placebo (p=0.029).

Adverse events that have been reported in clinical studies or post-marketing with irbesartan are categorized below according to the system organ class and frequency (see Table 3).

The following CIOMS frequency rating is used, when applicable:
Very common: (≥ 1/10); common: (≥ 1/100 to < 1/10); uncommon: (≥ 1/1 000 to < 1/100); rare: (≥ 1/10 000 to < 1/1 000); very rare: (< 1/10 000), unknown: cannot be estimated from available data.

The frequencies of adverse reactions from the post-marketing experience are unknown, because these reactions are reported voluntarily from a population of uncertain size.

Table 3 - Adverse Events Reported in Clinical Trials with Irbesartan or in Post-marketing Reports

	Common (a)	Uncommon (b)	Unknown
Blood and lymphatic system disorders			Anaemia, Thrombocytopenia (including thrombocytopenic purpura)
Immune system disorders			Hypersensitivity reactions (anaphylactic reactions including anaphylactic shock)
Metabolism and nutrition disorders			Hyperkalemia, hypoglycaemia.
Nervous system disorders	Dizziness, headache, orthostatic dizziness*		Vertigo

Cardiac disorders		Tachycardia	
Respiratory, thoracic and mediastinal disorders		Cough	
Gastrointestinal disorders	Nausea/vomiting	Diarrhea, dyspepsia / heartburn	dysgeusia
Hepatobiliary disorders		Jaundice	Elevated liver function tests, hepatitis
Skin and subcutaneous tissue disorders			Leukocytoclastic vasculitis, Angioedema, urticaria, photosensitivity, psoriasis (and psoriasis exacerbation)
Musculoskeletal and connective tissue disorders	Musculoskeletal pain		Myalgia, arthralgia, muscle cramps
Renal and urinary disorders			Impaired renal function including cases of renal failure in patients at risk
Reproductive system and breast disorders		Sexual dysfunction	
Ear and labyrinth disorders			Tinnitus
General disorders and conditions of the administration site	Fatigue, edema	Chest pain	Asthenia
Vascular disorders	orthostatic hypotension	Flushing	
Investigation	Very Common: Hyperkalaemia* occurred more often in diabetic patients treated with irbesartan than with placebo. In diabetic hypertensive patients with microalbuminuria and normal renal function, hyperkalaemia (≥ 5.5 mEq/L) occurred in 29.4% of the patients in the irbesartan 300 mg group and 22% of the patients in the placebo group. In diabetic hypertensive patients with chronic renal insufficiency and overt proteinuria, hyperkalaemia (≥ 5.5 mEq/L) occurred in 46.3% of the patients in the irbesartan group and 26.3% of the patients in the placebo group. Common: significant increases in plasma creatine kinase were commonly observed (1.7%) in irbesartan treated subjects. None of these increases were associated with identifiable clinical musculoskeletal events. In 1.7% of hypertensive patients with advanced diabetic renal disease treated with irbesartan, a decrease in haemoglobin*, which was not clinically significant, has been observed.		

a Including all adverse events, probably or possibly related, or indefinite relationship to the therapy, whatever its incidence in patients treated with placebo

b Including all adverse events, probably or possibly related, or indefinite relationship to the therapy, occurring with a frequency of 0.5% to <1% and in a similar or slightly higher incidence in patients treated with irbesartan compared to patients treated with placebo (none of them significantly different in statistical terms between the 2 treatment groups)

Terms marked with a star (*) refer to the adverse reactions that were additionally reported in > 2% of diabetic hypertensive patients with chronic renal insufficiency and overt proteinuria and in excess of placebo.

For amlodipine:

Adverse events reported in clinical studies with amlodipine are categorized below according to system organ class and frequency (see Table 4).
The following CIOMS frequency rating is used, when applicable:
Very common: (≥ 1/10); common: (≥ 1/100 to < 1/10); uncommon: (≥ 1/1 000 to < 1/100); rare: (≥ 1/10 000 to < 1/1 000); very rare: (< 1/10 000), unknown: cannot be estimated from available data.

Table 4 - Adverse Events Reported in Clinical Trials with Amlodipine

	Very Common	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic					Leukocytopaenia Thrombocytopenia	
Immune system disorders					Allergic reaction	
Metabolism and nutrition disorders					Hyperglycemia	
Psychiatric disorders			Depression, Insomnia, mood changes	Confusion		
Nervous system disorders		Dizziness Headache Drowsiness	Hypoesthesia, paresthesia, tremor, taste perversion, syncope, Peripheral neuropathy, Hypertonia, Extrapyramidal disorder			

Eye disorders		Visual disturbances (including diplopia)				
Ear and labyrinth disorders			Tinnitus			
Cardiac disorders		Palpitations	Arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)		Acute myocardial infarction	
Vascular disorders		Flushing	Hypotension		Vasculitis	
Respiratory, thoracic and mediastinal		Dyspnea	Coughing, rhinitis			
Gastrointestinal disorders		Nausea Abdominal pain Dyspepsia Altered bowel habits (including diarrhoea and constipation)	Vomiting, Dry mouth		Pancreatitis, gastritis, gingival hyperplasia	
Hepatobiliary disorders					Hepatitis Jaundice Hepatic enzyme elevations (mostly consistent with cholestasis)	

Skin and subcutaneous tissue disorders			Urticaria Pruritus Purpura Increased sweating Skin discoloration Alopecia Exanthem Hyperhidrosis		Angioedema Erythema multiforme Exfoliative dermatitis Stevens-Johnson syndrome Quincke's oedema Photosensitivity	Toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders			Arthralgia, muscle cramps, myalgia, back pain			
Renal and urinary disorders			Increased urinary frequency, micturition disorder, nocturia			
Reproductive system and breast disorders			Impotence, gynecomastia			
General disorders and administration site conditions	Edema	Fatigue Asthenia	Chest pain Malaise Non-specific pain			
Research			Weight increase Weight decrease			

In clinical studies comparing the fixed-dose combination irbesartan/amlodipine to either irbesartan or amlodipine monotherapy, the types and incidences of treatment-emergent adverse events (TEAEs) possibly related to study treatment were similar to those observed in earlier monotherapy clinical trials and post-marketing reports. The most frequently reported adverse event was peripheral edema, mainly associated with amlodipine (see Table 5).

The following CIOMS frequency rating is used, when applicable:
Very common ≥ 10 %; Common ≥ 1 and <10 %; Uncommon ≥ 0.1 and < 1 %; Rare ≥ 0.01 and < 0.1 %; Very rare < 0.01 %, Unknown (cannot be estimated from available data).

Table 5 - Treatment-Emergent Adverse Events Considered Possibly Related to Study Drug in Irbesartan/Amlodipine Clinical Studies (I-ADD, I-COMBINE and I-COMBO)		
	Common	Uncommon
Monotherapy with Irbesartan		

General disorders and conditions at the administration site		fatigue
Ear and labyrinth disorders	vertigo	
Nervous system disorders	dizziness	headache
Gastrointestinal disorders	upper abdominal pain, nausea, tongue disorder	diarrhea
Skin and subcutaneous tissue disorders		alopecia
Traumatic injuries, poisonings and complications of procedures		fall
Monotherapy with Amlodipine		
General disorders and conditions at the administration site	peripheral edema	edema, facial edema
Ear and labyrinth disorders		vertigo
Gastrointestinal disorders	glossodynia	
Nervous system disorders	dizziness	headache
Respiratory, thoracic and mediastinal disorders	cough	
Skin and subcutaneous tissue disorders	contact dermatitis	
Vascular disorders	hot flush	flushing
Fixed-dose Combination of Irbesartan/amlodipine		
General disorders and conditions at the administration site	peripheral edema, edema	asthenia
Ear and labyrinth disorders		vertigo
Cardiac disorders	palpitations	sinus bradycardia
Nervous system disorders	dizziness, headache, somnolence	paresthesia
Disorders of the reproductive system and mammary		erectile dysfunction
Respiratory, thoracic and mediastinal disorders		cough
Vascular disorders	Orthostatic hypotension	Hypotension

Gastrointestinal disorders	gingival swelling	nausea, upper abdominal pain, constipation
Renal and urinary disorders	proteinuria	azotemia, hypercreatininemia
Metabolism and nutrition disorders		hyperkalemia
Musculoskeletal and connective tissue disorders		joint stiffness, arthralgia, myalgia

INTERACTIONS WITH OTHER DRUGS AND OTHER FORMS OF INTERACTION:

For irbesartan and amlodipine combination: Based on a pharmacokinetic study where irbesartan and amlodipine were administered alone or in combination, there is no pharmacokinetic interaction between irbesartan and amlodipine.

No drug interaction studies have been conducted with Aprovasc® and other medicinal products.

For Irbesartan: Based on in vitro information, no interactions are expected with drugs whose metabolism is dependent on CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2D6, CYP2E1 or CYP3A4 cytochrome isoenzymes.

Irbesartan is primarily metabolized by CYP2C9, however, no significant interactions were observed during clinical interaction studies when irbesartan was administered concomitantly with warfarin (a drug metabolized by CYP2C9).

Diuretics and other antihypertensive agents: other antihypertensive agents may increase the hypotensive effects of irbesartan; however irbesartan has been safely administered with other antihypertensive agents, such as beta-blockers, long-acting calcium channel blockers, and thiazide diuretics. Prior treatment with high dose diuretics may result in volume depletion and a risk of hypotension when initiating therapy with Aprovasc® (see Special warnings and special precautions for use).

Irbesartan does not affect the pharmacokinetics of simvastatin (metabolized by CYP3A4) or digoxin (substrate of P-glycoprotein efflux transporter).

The pharmacokinetics of Irbesartan is not affected by concomitant administration of nifedipine or hydrochlorothiazide

The combination of APROVASC® with medications containing aliskiren is contraindicated in patients with diabetes mellitus or with moderate to severe renal failure (glomerular filtration rate (GFR) <60 mL/min/1.73 m2) and is not recommended in other patients.

Angiotensin-converting enzyme inhibitors (ACE inhibitors): The use of Aprovasc® in combination with ACE inhibitors is contraindicated in patients with diabetic nephropathy and is not recommended in other patients.

Repaglinide: Irbesartan has the potential to inhibit OATP1B1. In a clinical study, it was reported that irbesartan increased the C_{max} and the AUC of repaglinide (OATP1B1 substrate) 1.8 fold and 1.3 fold respectively when administered 1 hour before repaglinide. In another study, no relevant pharmacokinetic interaction was reported when two drugs were administered together. Therefore, it may be necessary to adjust the dose in antidiabetic treatment such as repaglinide (see General precautions).

Based on the experience with the use of other medications that affect the renin-angiotensin system, the concomitant use of Irbesartan with potassium-sparing diuretics, potassium supplements, potassium-containing salt substitutes, or other medications that may increase kalaemia with irbesartan can cause an increase in

serum potassium, sometimes severe, and requires close monitoring of serum potassium.

Non-steroidal anti-inflammatory drugs: when angiotensin II antagonists are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. selective COX-2 inhibitors, acetylsalicylic acid (> 3 g/day) and non-selective NSAIDs), attenuation of the antihypertensive effect may occur.
As with ACE inhibitors, concomitant use of angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

Lithium: increases in serum lithium concentrations and lithium toxicity have been reported with the concomitant use of Irbesartan. Therefore, this combination is not recommended (see Special warnings and precautions for use). If the combination proves necessary, careful monitoring of serum lithium levels is recommended.

For Amlodipine: Amlodipine has been safely administered concomitantly with thiazide diuretics, beta blockers, alpha blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual glyceryl trinitrate, non-steroidal anti-inflammatory drugs, and oral hypoglycemic drugs.
Data obtained from *in vitro* studies with human plasma show that amlodipine has no effect on protein binding of the medications studied (digoxin, phenytoin, warfarin or indomethacin).

Cimetidine:
Co-administration of amlodipine with cimetidine did not alter amlodipine pharmacokinetics.

Grapefruit juice:
The administration of amlodipine with grapefruit or grapefruit juice is not recommended as in some patients, its bioavailability may increase, resulting in an increase in the blood pressure lowering effects.

Sildenafil:
When using amlodipine and sildenafil in combination, each agent independently exerted its own blood pressure lowering effect.

Atorvastatin:
Simultaneous administration of multiple doses of 10 mg of amlodipine with 80 mg of atorvastatin showed no significant change in the steady-state pharmacokinetic parameters of atorvastatin.

Digoxin:
Simultaneous administration of amlodipine with digoxin did not modify serum digoxin levels or digoxin renal clearance in healthy volunteers.

Warfarin:
Simultaneous administration of amlodipine did not significantly modify the effect of warfarin on prothrombin time.

Effects of other medicinal products on amlodipine
CYP3A4 Inhibitors
Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides such as erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure. The clinical translation of these PK variations may be more pronounced in elderly subjects. Clinical monitoring and dose adjustment may be necessary.

Inducers of CYP3A4
Concomitant administration of inducers known as CYP3A4 may cause variations in plasma concentrations of amlodipine. Amlodipine should be used with caution when administered with CYP3A4 inducers. Blood pressure should be monitored and the dose considered should be adjusted during and after concomitant medication, particularly with potent CYP3A4 inducers (for example, rifampicin, hypericum perforatum).

Dantrolene (infusion)
In animals, fatal ventricular fibrillation and cardiovascular collapse have been observed in association with hyperkalaemia after intravenous administration of verapamil and dantrolene. Due to the risk of hyperkalaemia, it is recommended that concomitant administration of calcium channel blockers such as amlodipine should be avoided in patients susceptible to malignant hyperthermia and in the treatment of malignant hyperthermia.

Effects of amlodipine on other medicinal products
The blood pressure lowering effects of amlodipine are added to the blood pressure lowering effects of other medicinal products with antihypertensive properties.

Tacrolimus
There is a risk of an increase in tacrolimus blood levels when it is administered together with amlodipine, but the pharmacokinetic mechanism of this interaction is not fully understood. In order to avoid tacrolimus toxicity, administration of amlodipine in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and adjustment of the dose of tacrolimus when appropriate.

Mechanistic Target of Rapamycin (mTOR) Inhibitors
mTOR inhibitors such as sirolimus, temsirolimus, and everolimus are CYP3A substrates. Amlodipine is a weak CYP3A inhibitor. With concomitant use of mTOR inhibitors, amlodipine may increase the exposure of mTOR inhibitors.

Cyclosporine
No studies have been conducted on the pharmacological interaction between cyclosporine and amlodipine in healthy volunteers or other populations, except kidney transplant patients, where variable trough concentration increases (average 0% - 40%) of cyclosporine were observed. Consideration should be given for monitoring cyclosporine levels in kidney transplant patients being treated with amlodipine, and cyclosporine doses should be reduced where necessary.

Simvastatin
Concomitant administration of multiple doses of 10 mg of amlodipine with 80 mg of simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. Limit the dose of simvastatin in patients taking amlodipine to 20 mg per day.

Aluminium/magnesium (antacid)
The simultaneous administration of an antacid with aluminium/magnesium with a single dose of amlodipine had no significant effect on the pharmacokinetics of amlodipine.

Laboratory test abnormalities:

There were no clinically significant changes in laboratory parameters in controlled clinical studies with irbesartan in hypertensive patients. No special control of laboratory parameters is required in patients with essential hypertension receiving the treatment.

Special precautions related to the carcinogenic, mutagenic and teratogenic effects, and effects on fertility:

Irbesartan:

No evidence of carcinogenicity was observed when Irbesartan was administered at doses up to 500/1000 mg/kg/day in rats (males/females, respectively) and 1000 mg/kg/day in mice for two years. These doses produced a systemic exposure 4-25 times (rats) and 4-6 times (mice) greater than exposure in humans who received 300 mg daily.

Irbesartan was not mutagenic in a battery of *in vitro* tests (Ames microbial test, rat hepatocyte DNA repair test, mammalian V79 premature gene-mutation test). Irbesartan was negative in several tests for induction of chromosomal aberrations (*in vitro* human lymphocyte assay; *in vivo* mouse micronucleus study).

Fertility and reproduction were not affected in studies of male and female rats, even with doses that cause some parental toxicity (up to 650 mg/kg/day). No significant effects on the number of corpora lutea, implants or live fetuses were observed. Irbesartan did not affect the survival, development, or reproduction of the offspring.

Transient toxic effects (increased renal pelvic cavitation, hydroureter or subcutaneous edema) were observed in rat fetuses at doses of 50 mg/kg/day or higher, which resolved after birth. In rabbits, maternal mortality, abortion and early fetal resorption were observed at doses of 30 mg/kg/day. No other teratogenic effects were observed in rats or rabbits.

Amlodipine:

Carcinogenesis: Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25 and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats, double* the maximum recommended clinical dose of 10 mg on a mg/m2 basis) was close to the maximum tolerated dose for mice but not for rats.

Mutagenesis: Mutagenicity studies did not reveal any effect related to amlodipine at either the gene or chromosome levels.

Infertility: There was no effect on fertility in rats treated with amlodipine (males for 64 days and females 14 days before mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m2 basis).

In another study in rats in which the male rats were treated with amlodipine besylate for 30 days at a dose comparable to the dose in humans based on mg/kg, a reduction in plasma follicle-stimulating hormone and testosterone levels was seen, in addition to a reduction in the density of spermatozoids and in the number of mature spermatids and Sertoli cells.

* Based on a 50 kg patient.

SIGNS AND MANAGEMENT OF OVERDOSAGE OR ACCIDENTAL INTAKE:

Experience in adults exposed to Irbesartan doses up to 900 mg/day for 8 weeks revealed no toxicity. No specific information is available on the treatment of overdosage with irbesartan. The information available on the overdose of amlodipine suggests that it could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension and shock with fatal prognosis have been reported. Close monitoring of patient should be done and treatment should be symptomatic and supportive.

Suggested measures include gastric lavage. Administration of activated charcoal to healthy individuals immediately or up to two hours after the ingestion of 10mg amlodipine has shown a significant decrease in the absorption of amlodipine.
As amlodipine is highly protein bound and irbesartan is not removed from the body by hemodialysis, hemodialysis does not seem to offer any benefit..

If massive overdose occurs, initiate active cardiorespiratory monitoring. Frequent measurement of blood pressure is essential. Clinically significant hypotension due to amlodipine overdose requires active cardiovascular support including limb elevation and monitoring of circulating fluid volume and urine output. A vasoconstrictor can help restore vascular tone and blood pressure, provided that there is no contraindication to its use.

Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

PRESENTATIONS:

Cardboard box with 14 or 28 tablets in blister packs.
Irbesartan 150 mg and amlodipine 5 mg (7 mg of amlodipine besilate)
Irbesartan 300 mg and amlodipine 5 mg (7 mg of amlodipine besilate)
Irbesartan 300mg and amlodipine 10 mg (14 mg of amlodipine besilate)

Nature and contents of container
14 or 28 tablets, packed in PVC/PE/PVDC/Aluminium blister and introduced in cardboard box. Not all pack sizes may be marketed.

Storage condition
Store below 30°C.

Shelf life
Please refer to outer box packaging for more information

NAME AND ADDRESS OF MANUFACTURER:

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