QUALITATIVE AND QUANTITATIVE COMPOSITION

Aprovasc® film coated tablet 150 mg/5 mg
Each tablet contains 150 mg Irbesartan and 5 mg of amlodipine
Aprovasc® film coated tablet 150 mg/10 mg
Each tablet contains 150 mg Irbesartan and 10 mg of amlodipine
Aprovasc® film coated tablet 300 mg/5 mg
Each tablet contains 300 mg Irbesartan and 5 mg of amlodipine
Aprovasc® film coated tablet 300 mg/10 mg
Each tablet contains 300 mg Irbesartan and 10 mg of amlodipine

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 150 mg/10 mg
Pink, oval shaped film coated tablets with '150/10' 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.

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 pharmacodynamics properties of each drug, Irbesartan and amlodipine, provide an addition of antihypertensive effects when administered in combination against the effect observed with both components 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 receptors (subtype AT1). Angiotensin II is an important component of the renin-angiotensin system, it participates in the pathophysiology of hypertension and sodium homeostasis. Irbesartan does not require metabolic activation for its action.

Irbesartan blocks the potent vasoconstriction and aldosterone-secreting effects produced by the 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 of 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.

Pharmacodynamics properties: The effect on the decrease in blood pressure by Irbesartan becomes apparent after the first dose and is present in an important way for 1-2 weeks; the maximum effect occurs in 4-6 weeks. In long-term follow-up studies, the effect of Irbesartan remained for more than a 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 mmHg (systolic/diastolic) higher figures 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 24hours 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.

Irbesartan blood pressure decreasing effects and the effects of thiazide-type diuretics are added. In patients who are not adequately controlled with 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 trough compared to 7-10/3-6 mmHg placebo (systolic/diastolic).

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 was administered concomitantly with hydrochlorothiazide at low doses (12.5 mg daily), the antihypertensive response in black patients was 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 calcium dihydropyridine antagonist (calcium ion antagonist or slow channel blocker) who inhibits the entry of calcium ions and the transmembrane influx of these ions into both the cardiac smooth muscle and the vascular smooth muscle. Amlodipine antihypertensive action mechanism is due to a direct relaxing 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, in this way, 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 dilation 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).

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

In patients with angina, the administration of amlodipine once a day increases the total time of exercise, the time for the onset of angina and the time for a depression of 1 mm in the ST segment. In addition, it decreases both the frequency of angina attacks 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.

Use in patients with hypertension
A randomised, double-blind study of morbidity and mortality called the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) was conducted to compare the new pharmacological treatments: amlodipine 2.5-10 mg/day (calcium-channel blocker) or lisinopril 10-40 mg/day (ACE inhibitor) as first-line thiadiuretic treatment, chlortalidone 12.5-25 mg/day for mild-to-moderate hypertension.

A total of 33,357 hypertensive patients aged 55 years and above were randomised and monitored for an average of 4.9years.
Patients had at least one additional risk factor for coronary artery disease, including: previous myocardial infarction or cerebrovascular accident (> 6 months before enrolment) or a record of another CHD with atherosclerosis (51.5% overall), type 2 diabetes (36.1%), C-HDL < 35 mg/dL (11.6%), left ventricular hypertrophy diagnosed by electrocardiogram or echocardiogram (20.9%), current smoker (21.9%).

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

Use in patients with heart failure
In haemodynamic studies and controlled clinical studies based on exercise in patients with NYHA class II-IV heart failure, it has been shown that amlodipine does not lead to clinical deterioration determined by tolerance to exercise, left ventricular ejection fraction and clinical symptoms.

A placebo-controlled study (PRAISE) designed to evaluate patients with NYHA class III-IV heart failure receiving digoxin, diuretics and ACE inhibitors, showed that amlodipine does not lead to an increased risk of mortality or combined mortality and morbidity with heart failure. In a large-scale, placebo-controlled follow-up study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure without clinical symptoms or objective findings of suggestive or underlying ischaemic disease, at stable doses of ACE inhibitors, digitalis and diuretics, amlodipine had no effect on overall cardiovascular mortality. In this same population, amlodipine was associated with more reports of pulmonary oedema.

Paediatric population: In a study involving 268 children aged between 6 and 17 years with predominantly secondary hypertension, the comparison of one dose of 2.5 mg and one dose of 5.0 mg of amlodipine with placebo, showed that both doses reduced systolic artery pressure significantly more than the placebo. The difference between the doses was not statistically significant. The long-term effects of amlodipine on growth, puberty and overall development have not been studied. The long-term efficacy of amlodipine treatment in childhood in reducing cardiovascular morbidity and mortality in adulthood has also not been established.

CLINICAL EFFICACY/CLINICAL STUDIES

The clinical evidence of efficacy of the Irbesartan and amlodipine fixed-dose combination derives from two studies: I-ADD and I-COMBINE. Both were multicenter, prospective, randomized, open, parallel groups, with blind evaluation of the endpoints. 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 5 mg 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 after Period A to receive 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 after Period A to receive 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 in Week 5. Secondary endpoints were diastolic blood pressure (DBP), measured at home 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 average of 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 with respect to amlodipine or Irbesartan alone (see Tables 1 and 2).

Table 1: I-ADD Adjusted changes means in blood pressure values from baseline assessment (mmHg)			
	Fixed-dose combination (N=155)	Monotherapy with Irbesartan(N=165)	

BP in mmHg	Adjusted change mean from baseline assessment (SE)	Adjusted change mean from baseline assessment (SE)	Mean difference adjusted 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 patients in the monotherapy group

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

	Fixed-dose combination (N=144)	Amlodipine (N=143)		
BP in mmHg	Adjusted change mean from baseline assessment (SE)	Adjusted change mean from baseline assessment (SE)	Mean difference adjusted 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 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 from 1.5 to 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 in the liver via glucuronide conjugation and oxidation. Its main circulating metabolite is irbesartan glucuronide (approximately 6%). Irbesartan conjugation and oxidation, mainly 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 radioactivity administered 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 Irbesartan without change.

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 to 3.5 mL/min are by renal clearance. Irbesartan exhibits a linear pharmacokinetics over the limits of the therapeutic dose. Steady-state plasma concentrations are reached within three days of the start of the once a day dosing regimen. The limited accumulation (<20%) was observed in plasma when the daily dose was repeated.

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

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 to 50%

higher than those observed in the younger subjects (18 to 40 years old). Regardless of age, the elimination half-life is similar.

No significant differences have been observed related to age regarding the clinical effect.

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 basically 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 maximum blood levels between 6 to 12 hours after dose administration. It has been estimated that the absolute bioavailability is 64 to 90%. 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 in consistency with the dosage once a day. Amlodipine is extensively metabolized by the liver forming inactive metabolites, 10% of the original compound and 60% as metabolites excreted in the urine.

Use in the elderly: The time to obtain the maximum plasma concentrations of amlodipine is similar between 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 increased AUC and elimination half-life in patients with congestive heart failure were as hoped for the age group studied.

The increases in the AUC and in the mean route of elimination in patients with congestive heart failure occurred as expected in this age group.

Pediatric patients: A pharmacokinetic study has been conducted in 74 hypertensive children between 12 months to 17 years of age (with 34 patients from 6 to 12 years of age and 28 patients from 13 to 17 years of age) receiving amlodipine doses between 1.25 and 20 mg administered once a day or twice a day.

In children 6 to 12 years of age and adolescents 13-17 years of age, typical oral clearance (CL/F) was 22.5 and 27.4 L/h respectively in male individuals and 16.4 and 21.3 L/h respectively in the female individuals. A great variability in exposure among people was observed. The data reported in children under 6 years of age are limited.

Patients with liver failure: Very limited clinical data exists on the administration of amlodipine in patients with liver failure. Patients with liver failure have reduced amlodipine clearance, resulting in a longer half-life and an increase in the AUC of approximately 40-60%.

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 speed and of absorption degree.

When administered separately or concomitantly at 300 mg and 10 mg dose levels, the time until the average plasma peak concentrations of Irbesartan and amlodipine remains 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 drugs are administered alone or concomitantly.

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).

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

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 angina)
- Haemodynamically unstable heart failure following an acute myocardial infarction.
- Severe hypotension
- Pregnancy and lactation (see *Warnings and Precautions for Use (Warnings)* and *Restrictions during 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 m^2).

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

WARNINGS AND PRECAUTIONS FOR USE
Warnings:

- ***Hypotension – Patients with volume depletion***
  Irbesartan has rarely been associated with hypotension in hypertensive patients who have no other concomitant condition. Symptomatic hypotension may occur, such as with ACE inhibitors, 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® or the start of treatment with the lowest possible dose should be considered.

- ***Hypoglycaemia***
  Irbesartan can cause hypoglycaemia, particularly in patients being treated for diabetes. Therefore, it may be necessary to adjust the dose of the diabetes medication of repaglinide or insulin (see *Side Effects and Adverse Reactions*).

- ***Fetal/neonatal morbidity and mortality***
  Although there is no experience with Irbesartan in pregnant women, it has been reported that exposure of the pregnancy product to ACE inhibitors, administered to pregnant women during the second and third quarters of pregnancy, causes injuries and death of the fetus. Therefore, as any other drug acting directly on the renin-angiotensin-aldosterone system, Aprovasc® should not be

administered during pregnancy. When 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 large-scale, 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 there having been no significant difference in the frequency of cases in which the heart failure worsened when compared with the placebo (see *Pharmacokinetics and Pharmacodynamics*). Calcium-channel blockers, including amlodipine, must be used with caution in patients with congestive heart failure, since they can increase the risk of future cardiovascular problems, events and mortality.

- ***Hepatic impairment:***

  For amlodipine
  As is the case with other calcium antagonists, the half-life of amlodipine is increased and the AUC values are greater in patients with abnormal liver function and dose recommendations have not been established for this group. Therefore, amlodipine must be initiated in the lowest possible dose range and should be used with caution, both as initial treatment and on increasing the dose in these patients. A slow dose adjustment and careful monitoring of patients with severe liver failure may be necessary.

- ***Elderly patients***
  In elderly patients, the dose must be increased carefully *(see Dosage and Method of Administration)*.

- ***Patients with renal failure***
  Amlodipine may be used in these patients at normal doses. The changes in amlodipine concentration in plasma are not correlated with the severity of the kidney failure. Amlodipine is not capable of being dialysed

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

Precautions:

Dual blockade of the Renin-Angiotensin-Aldosterone system, (RAAS)
The dual blockade of the renin angiotensin aldosterone system with the combination of APROVASC® with angiotensin-converting enzyme inhibitors (ACEIs) or with aliskiren is not recommended since there is an increased risk of hypotension, hyperkalemia, and changes in renal function compared to monotherapy.

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.

- ***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 stenosis of the renal artery of 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 elevation 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.

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

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. In patients receiving 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.

- **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. Lithium levels should be monitored in patients who are receiving APROVASC.

- **Effects of Irbesartan on ability to drive**

For Irbesartan: The effect of Irbesartan on the ability to drive and use machines has not been investigated, despite the fact that, based on its pharmacodynamic properties, it is unlikely that Irbesartan will have an effect on the ability to drive or operate machines, you must bear in mind 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 with a potential risk of pregnancy 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 Warning and Precautions for Use (*Warnings*))*.

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

For amlodipine: Amlodipine is excreted in breast milk. The amount of the mother's dose received by the baby is estimated to be in the interquartile range of 3 to 7%, up to a maximum of 15%. The effect of amlodipine in infants is unknown.

There have been reports of reversible biochemical changes in the heads of spermatozoids in some patients treated with calcium channel blockers. There is not sufficient clinical data to determine the possible effect of amlodipine on fertility. A study in rats showed adverse effects on male fertility.

SIDE-EFFECTS AND ADVERSE REACTIONS:

ADVERSE EVENTS:

Since clinical studies are conducted under broadly variable conditions, the degree 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 5,000 subjects, including 1,300 hypertensive patients treated for 6 months and more than 400 patients treated for a 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 the placebo-controlled clinical trials, including 1,965 patients treated with Irbesartan (usual treatment duration of 1 to 3 months), the discontinuation of treatment due to some 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 listed below according to the organ system 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: no data available on its incidence.

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

Table 3 - Adverse Events Reported in clinical trials with Irbesartan or in post-marketing reports

	Common (a)	Uncommon (b)	Not known
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	
Cardiac disorders		Tachycardia	
Respiratory, thoracic and mediastinal disorders		Cough	
Gastrointestinal disorders	Nausea/vomiting	Diarrhea, dyspepsia / heartburn	
Hepatobiliary disorders			Jaundice, elevated liver function tests, hepatitis
Skin and subcutaneous tissue disorders			Angioedema, urticaria, photosensitivity, psoriasis (and psoriasis exacerbation)
Musculoskeletal and connective tissue disorders			Myalgia
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

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

b *Includes all adverse events, probably or possibly related, or of indefinite relationship with 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)*

For amlodipine:

Adverse events reported in clinical studies with amlodipine are listed below according to organ system 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: no data available on its incidence.

Table 4: Adverse Events Reported in clinical trials with amlodipine

	Very Common	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders					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		Hypertonia Peripheral neuropathy	Extrapyramidal disorder

Sight 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 disorders		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 combination of Irbesartan/amlodipine fixed dose with Irbesartan or amlodipine monotherapy, the types and incidences of adverse events arising from treatment (TEAEs) possibly related to study treatment were similar to those observed in the first clinical studies on monotherapy and in 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 calculated from the 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

Metabolic and nutritional 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 metabolized mainly by CYP2C9, however, no significant interactions were observed during clinical interaction studies when Irbesartan was administered concomitantly with warfarin (a drug metabolized by CYP2C9).

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 m^2) and is not recommended in other patients.

Angiotensin-converting enzyme inhibitors (ACE inhibitors): 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 Cmax 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.

In elderly patients with volume depletion (including those on treatment with diuretics), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with angiotensin II receptor antagonists, including Irbesartan, can cause impaired renal function, including possible acute renal failure. These effects are usually reversible. Renal function should be monitored periodically in patients receiving periodic treatment with Irbesartan and NSAIDs. The antihypertensive effect of angiotensin II receptor antagonists, including Irbesartan, may be attenuated by NSAIDs including selective COX-2 inhibitors.

Lithium: Increases in serum lithium concentrations and lithium toxicity has been reported with the

concomitant use of Irbesartan. Monitor levels in patients receiving Irbesartan and lithium.

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 with 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 reductive 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 of atorvastatin pharmacokinetic parameters.

Digoxin: Simultaneous administration of amlodipine with digoxin did not modify serum concentrations of digoxin or its 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 inhibitors of CYP3A4 (protease inhibitors, azole antifungals, macrolides such as erythromycin or clarithromycin, verapamil or diltiazem) may give rise to a 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; therefore, 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 reducing effects of amlodipine are added to the blood pressure reducing effects of other medicinal products with antihypertensive properties.

Tacrolimus:
There is a risk of an increase in blood tacrolimus 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 the levels of tacrolimus in the blood and adjustment of the dose of tacrolimus where appropriate.

Molecular 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 they vary. Increases have been seen in the minimum concentration (average 0% - 40%) of cyclosporine. Monitoring should be considered to control 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.

ALTERATIONS IN THE RESULTS OF LABORATORY TESTS

There were no clinically significant changes in laboratory parameters in clinical studies controlled 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 500/1,000 mg/kg/day in rats (males/females, respectively) and 1,000 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 (human lymphocyte assay, *in vitro*; mouse micronucleus study, *in vivo*).

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

At doses of 50 mg/Kg/day and greater, transient effects (increased renal pelvic cavitation, hydroureter or subcutaneous edema) were observed in the fetuses of rats, which resolved after birth. In rabbits, maternal mortality, abortion and early fetal resorption were observed, with a dose 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/m^2 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 gene or chromosome level.

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 in mg/m^2 base).

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 of follicle-stimulating hormone and testosterone levels was seen, in addition to a reduction in the density 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 with adults exposed to Irbesartan doses up to 900 mg/day for 8 weeks did not reveal toxicity. No specific information is available about 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. The administration of activated carbon to healthy individuals immediately or up to two hours after the ingestion of 10 mg of 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 with 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 volume and urinary output. A vasoconstrictor can help restore vascular tone and blood pressure, when there is no contraindication to its use.

Intravenous calcium gluconate may be of benefit 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
Irbesartan 150 mg and amlodipine 10 mg
Irbesartan 300 mg and amlodipine 5 mg
Irbesartan 300 mg and amlodipine 10 mg.

Nature and contents of container

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

NAME AND ADDRESS OF MANUFACTURER:
Sanofi-aventis de México, S.A. de C.V.
Acueducto del Alto Lerma No. 2
Zona Industrial Ocoyoacac,
C. P. 52740 Ocoyoacac, México

Date of revision: Dec 2022 (CCDS V10 11 12 based on Mexico SmPC Nov 2020)