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 pharmacodynamic properties of each drug, irbesartan and amlodipine, provide an additive antihypertensive effect when administered in combination compared to the effect of each drug administered separately. Both AT1 receptor antagonists and calcium channel blockers lower blood pressure by reducing peripheral resistance, but calcium influx blockade and reduction of angiotensin II vasoconstriction are complementary mechanisms.

Irbesartan:

Mechanism of action: Irbesartan is a specific angiotensin II receptor antagonist (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 to exert its effect.
Irbesartan blocks the potent vasoconstrictor and aldosterone-secreting effects of angiotensin II by selective antagonism of angiotensin II receptors (AT1 subtype) located on vascular smooth muscle cells and the adrenal cortex. Irbesartan has no agonist activity at the AT1 receptor and has a much greater affinity (more than 8500-fold) for the AT1 receptor than for the AT2 receptor (receptor that has not been shown to be associated with cardiovascular homeostasis).

Irbesartan does not inhibit enzymes involved in the renin-angiotensin system (i.e., angiotensin converting enzyme [ACE]) or have an effect on other hormone receptors or ion channels involved in the cardiovascular regulation of blood pressure and sodium homeostasis. Irbesartan AT1 receptor blockade disrupts the renin-angiotensin feedback loop, increasing plasma renin and angiotensin II levels. Following irbesartan administration, aldosterone plasma concentrations decrease; however, no significant effect on serum potassium levels can be observed at the recommended doses (mean increase <0.1 mEq/L). Irbesartan has no notable effect on serum triglycerides, cholesterol or glucose concentrations; it has no effect on serum uric acid levels or on urinary uric acid excretion.

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

A single dose of up to 900 mg per day produced a dose-dependent decrease in blood pressure. Once daily doses of 150-300 mg decrease trough supine or seated blood pressures (i.e., 24 hours after dosing) by an average of 8-13/5-8 mm Hg (systolic/diastolic), which is higher than that observed with placebo. The effects measured at trough are 60-70% of the corresponding peak diastolic and systolic effects. Optimal effects on 24-hour blood pressure are achieved with once daily dosing.

Blood pressure is lowered to about the same extent in both standing and supine positions. Orthostatic effects are infrequent, but as with ACE inhibitors, may be expected to occur in sodium- and/or volume-depleted patients.

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

Neither age nor gender has an effect on irbesartan efficacy. As is the case with other drugs that have an effect on the renin-angiotensin system, black patients have a notably lower response to irbesartan monotherapy. When irbesartan is administered concomitantly with low-dose hydrochlorothiazide (e.g., 12.5 mg daily), the antihypertensive response in black patients is similar to that in white patients.

After withdrawal of irbesartan, blood pressure gradually returns to 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 transmembrane influx of calcium ions into cardiac and vascular smooth muscle. The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which amlodipine relieves angina symptoms has not been determined but amlodipine reduces total ischemic burden in the following two ways:

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

2) The mechanism of action of amlodipine also probably involves dilatation of the main coronary arteries and arterioles, both in normal and ischemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina).

Pharmacodynamic properties: In patients with hypertension, once daily dosing produces significant reductions of blood pressure in both the supine and standing positions over a period of 24 hours. Due to the slow onset of action, acute hypotension is not associated with amlodipine administration.

In patients with angina, once daily administration of amlodipine increases total exercise time, time to angina onset, and time to 1 mm ST segment depression. In addition, it decreases both angina attack frequency and glyceryl trinitrate tablet consumption.

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:

Concomitant administration of irbesartan and amlodipine, whether in a fixed dose combination tablet or the free combination, has no effect 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 the 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 given separately or concomitantly at 300 mg and 10 mg dose levels, time to mean peak plasma concentrations of irbesartan and amlodipine remain unchanged, i.e. 0.75-1 hour and 5 hours after administration, respectively. Similarly, Cmax and AUCs are in the same range resulting in a relative bioavailability of 95% for irbesartan and 98% for amlodipine whether the two drugs are administered concomitantly.

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

The pharmacokinetic profile of both drugs appears to be linear over the co-administered dose range (i.e. between 150 mg and 300 mg for irbesartan, and between 5 mg and 10 mg for amlodipine).

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

CLINICAL EFFICACY/CLINICAL STUDIES

The clinical evidence for the efficacy of the fixed-dose combination of irbesartan and amlodipine is derived from two studies: the I-ADD and I-COMBINE studies. Both studies were multi-center, prospective, randomized,

open-label, parallel-group studies with blinded endpoint evaluation design. The studies were conducted in patients with established essential hypertension, having uncontrolled blood pressure (mean systolic blood pressure [SBP] ≥145 mmHg) after at least four 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 amlodipine 5 mg or irbesartan 150 mg, once daily, for seven to ten days. At the end of Period A, if a patient's mean SBP was <135 mmHg, he or she was withdrawn from the respective study.

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

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

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

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

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

	Irbesartan/amlodipine Fixed-dose combination (N=155)	Irbesartan Monotherapy (N=165)		
BP in mmHg	Adjusted mean change from baseline (SE)	Adjusted mean change from baseline (SE)	Adjusted mean difference between groups (SE)	p-value
Week 5				
Home SBP (n= 153/163)	-15.4 (0.8)	-5.6 (0.8)	-9.8 (1.1)	p<0.001
Home DBP (n= 153/163)	-7.4 (0.5)	-2.4 (0.5)	-5.0 (0.7)	p<0.001
Office SBP (n=154/164)	-14.7 (1.0)	-5.1 (1.0)	-9.6 (1.4)	p<0.001
Office DBP (n= 154/164)	-7.3 (0.7)	-2.4 (0.6)	-4.9 (0.9)	p<0.001
Week 10				

Home SBP* (n= 146/153)	-18.7 (0.8)	-9.9 (0.8)	-8.8 (1.1)	p<0.001
Home DBP (n= 146/153)	-8.6 (0.5)	-3.9 (0.5)	-4.7 (0.7)	p<0.001
Office SBP (n= 149/162)	-17.9 (1.2)	-8.4 (1.1)	-9.5 (1.6)	p<0.001
Office DBP (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 group/number of evaluable patients in monotherapy group				

Table 2 - I-Combine – Adjusted mean changes in blood pressure from baseline (mmHg) – ITT Population				
	Irbesartan/amlodipine Fixed-dose combination (N=144)	Amdolipine Monotherapy (N=143)		
BP in mmHg	Adjusted mean change from baseline (SE)	Adjusted mean change from baseline (SE)	Adjusted mean difference between groups (SE)	p-value
Week 5				
Home SBP (n= 141/139)	-12.4 (0.7)	-6.3 (0.7)	-6.2 (1.0)	p<0.001
Home DBP (n= 141/139)	-5.6 (0.5)	-3.0 (0.5)	-2.6 (0.7)	p<0.001
Office SBP (n=143/143)	-10.8 (1.0)	-3.3 (1.0)	-7.4 (1.4)	p<0.001
Office DBP (n= 143/143)	-3.8 (0.6)	-1.2 (0.6)	-2.6 (0.9)	P=0.004
Week 10				
Home SBP* (n= 132/131)	-18.1 (0.7)	-13.5 (0.7)	-4.5 (1.0)	p<0.001
Home DBP (n= 132/131)	-9.4 (0.5)	-6.2 (0.5)	-3.2 (0.7)	p<0.001
Office SBP (n= 134/136)	-18.4 (1.1)	-12.4 (1.1)	-6.0 (1.6)	p<0.001
Office DBP (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 fixed-dose combination group/number of evaluable patients in monotherapy group

Pharmacokinetics properties
Irbesartan:
Irbesartan is an orally active agent that does not require biotransformation to exert its effect. Following oral administration, irbesartan is rapidly and completely absorbed. Peak plasma concentrations are reached 1.5-2 hours after oral administration. The absolute oral bioavailability of irbesartan is 60-80%. Food has no effect on irbesartan bioavailability.

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

In plasma, unchanged irbesartan accounts for 80-85% of the circulating radioactivity following oral or intravenous administration of 14C-labeled irbesartan. 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 isoenzyme CYP3A4 has a negligible effect. Irbesartan is not metabolized by most isoenzymes commonly involved in drug metabolism (i.e., CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2D6, or CYP2E1), and it does not significantly induce or inhibit these enzymes. Irbesartan does not induce or inhibit the isoenzyme CYP3A4.

Irbesartan and its metabolites are eliminated by both the biliary and renal routes. About 20% of the administered radioactivity after administration of either an oral or intravenous dose of 14C-labeled irbesartan is recovered in urine, with the remainder recovered in the feces. Less than 2% of the dose is excreted in the urine as unchanged irbesartan.

The terminal elimination half-life (t1/2) of irbesartan 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 linear pharmacokinetics over the therapeutic dose range. Steady-state plasma concentrations are reached within three days after initiation of a once-daily dosing regimen. Limited accumulation (<20%) is observed in plasma after repeated once-daily dosing.

In hypertensive subjects, higher irbesartan plasma concentrations were observed in females compared to males (11-44%). Following multiple dosing, however, no differences in either accumulation or elimination half-life were observed between males and females. No gender-specific differences in clinical effect have been observed.

In elderly normotensive subjects (males and females, 65-80 years) with clinically normal renal and hepatic function, irbesartan plasma AUC and peak plasma concentrations (Cmax) were approximately 20-50% higher than in younger subjects (18-40 years). Regardless of age, elimination half-life is comparable.

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

In black and white normotensive subjects, irbesartan plasma AUC and t1/2 are approximately 20-25% higher in black subjects compared to white subjects, whereas irbesartan peak plasma concentrations (Cmax) were essentially equivalent.

In patients with renal impairment (regardless of degree) and in hemodialysis patients, the pharmacokinetic profile of irbesartan is not significantly altered. Irbesartan is not removed by hemodialysis.

In patients with hepatic insufficiency due to mild to moderate cirrhosis, the pharmacokinetic profile of irbesartan is not significantly altered.

Amlodipine:
After oral administration of therapeutic doses, amlodipine is well absorbed, with peak blood levels reached between 6 and 12 hours post administration. Absolute bioavailability is estimated to be between 64 and 90%. The volume of distribution of amlodipine is approximately 21 L/kg. *In vitro* studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma protein. Food intake does not have an effect on amlodipine absorption.

The terminal plasma elimination half-life is about 35–50 hours and is compatible with once daily dosing. 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 elderly patients: The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to decrease, resulting in increases in AUC and elimination half-life in elderly patients.

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

Pediatric patients: A population PK study has been conducted in 74 hypertensive children aged from 12 months to 17 years (with 34 patients aged 6 to 12 years and 28 patients aged 13 to 17 years) receiving amlodipine doses of between 1.25 and 20 mg given either once or twice daily.

In children 6 to 12 and in adolescents 13-17 years of age the typical oral clearance (CL/F) was 22.5 and 27.4 L/h, respectively, in males and 16.4 and 21.3 L/h, respectively, in females. Large variability in exposure between individuals was observed. Data reported in children younger than 6 years are limited.

Patients with hepatic insufficiency: see Warnings.

CONTRAINDICATIONS:
As the drug contains both irbesartan and amlodipine, Aprovasc® is contraindicated in:

- patients allergic to either or both of the active substances or to any of the ingredients of the drug
- patients allergic to dihydropyridines
- patients with cardiogenic shock, clinically significant aortic stenosis, unstable angina (excluding Prinzmetal's angina)
- pregnancy and lactation (see Warnings and Pregnancy and Lactation).

Aprovasc® should not be co-administered with medicinal products containing aliskiren in patients with diabetes or moderate to severe renal insufficiency (glomerular filtration rate [GFR] < 60 mL/min/1.73 m2).

Aprovasc® should not be co-administered with angiotensin-converting enzyme (ACE) inhibitors in patients with diabetic nephropathy.

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

Hypotension: Volume-Depleted Patients: Irbesartan has been rarely associated with hypotension in hypertensive patients without other co-morbid conditions. As with ACE inhibitors, symptomatic hypotension may be expected to occur in sodium/volume-depleted patients such as those treated vigorously with diuretics and/or salt restriction, or on hemodialysis. Volume and sodium-depletion should be corrected before initiating therapy with Aprovasc® or a lower starting dose should be considered.

Fetal/neonatal morbidity and mortality: Although there is no experience with irbesartan in pregnant women, *in utero* exposure to ACE inhibitors given to pregnant women during the second and third trimesters of gestation has been reported to cause injury and death to the developing fetus. Thus, as for any drug that also acts directly on the renin-angiotensin-aldosterone system, Aprovasc® should not be used during pregnancy. If pregnancy is detected during therapy, Aprovasc® should be discontinued as soon as possible.

Patients with heart failure: In a long-term, placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure of nonischemic etiology, amlodipine was associated with increased reports of pulmonary edema despite no significant difference in the incidence of worsening heart failure as compared to placebo (see Pharmacodynamics).

Hepatic impairment:
As with other calcium antagonists, amlodipine's half-life is prolonged in patients with impaired liver function and dosage recommendations have not been established. Aprovasc® should therefore be administered with caution in these patients.
Hypertensive crisis:
The safety and efficacy of Aprovasc® in hypertensive crisis has not been established.

General precautions:

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. 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: Among patients who received irbesartan in clinical studies, no overall differences in efficacy or safety were observed between older patients (65 years or older) and younger patients.

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

FERTILITY, PREGNANCY AND LACTATION
Pregnancy*:* There are no adequate and well-controlled studies in pregnant women. Aprovasc® is contraindicated during pregnancy. Aprovasc® must not be administered to women of childbearing potential unless effective contraception is used. When pregnancy is detected during treatment, Aprovasc® should be discontinued as soon as possible (see Contraindications and Warnings).

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

SIDE-EFFECTS AND ADVERSE REACTIONS:
Adverse events:

Because clinical trials are conducted under widely varying conditions, the incidence of adverse reaction observed in the clinical trials of one drug cannot be directly compared to that observed in the clinical trials of other drugs and may not reflect that observed in practice.

Irbesartan has been evaluated for safety in approximately 5000 subjects in clinical studies, including 1300 hypertensive patients treated for 6 months and more than 400 patients treated for 1 year or more. Adverse events in patients receiving irbesartan were generally mild and transient with no relationship to the dose administered. The incidence of adverse events was not related to age, gender or race.

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

Adverse events that have been reported in clinical trials or postmarketing experience with irbesartan are categorized below according to system organ class and frequency (see Table 3).

The frequency of adverse events is defined using the following convention:
Very common: (≥ 1/10); common: (≥ 1/100 to < 1/10); uncommon: (≥ 1/1 000 to < 1/100); rare: (≥ 1/10 000 to < 1/1 000); very rare: (< 1/10 000), unknown: no incidence data available.

Frequencies of adverse reactions from postmarketing experience are unknown, as these reactions are reported voluntarily from a population of uncertain size.

Table 3 - Adverse Events Reported in Irbesartan Clinical Trials or Postmarketing Reports

	Common (a)	Uncommon (b)	Unknown
Immune system disorders			Hypersensitivity reactions
Metabolism and nutrition disorders			Hyperkalemia
Nervous system disorders	Dizziness, headache	Postural 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
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 administration site conditions	Fatigue, edema	Chest pain	Asthenia

a Includes all adverse events whether causal relationship to therapy is probable, possible or unlikely, irrespective of incidence in the placebo-treated patients

b Includes all adverse events, whether causal relationship to therapy is probable, possible or unlikely, occurring with an incidence of 0.5% to <1% and at similar or slightly increased incidence in irbesartan- treated patients compared to placebo-treated patients (no statistically significant differences between the 2 treatment groups)

For amlodipine:

Adverse events that have been reported in amlodipine trials are categorized below according to system organ class and frequency (see Table 4).
The frequency of adverse events is defined using the following convention:
Very common: (≥ 1/10); common: (≥ 1/100 to < 1/10); uncommon: (≥ 1/1 000 to < 1/100); rare: (≥ 1/10 000 to < 1/1 000); very rare: (< 1/10 000), unknown: no incidence data available.

Adverse events that have been reported in amlodipine trials are categorized below according to system organ class and frequency (see Table 4).

The frequency of adverse events is defined using the following convention:

Very common: (≥ 1/10); common: (≥ 1/100 a < 1/10); uncommon: (≥ 1/1,000 a < 1/100); rare: (≥ 1/10,000 a < 1/1,000); very rare: (< 1/10,000), unknown: no incidence data available.

Table 4 - Adverse Events Reported in Amlodipine Clinical Trials

	Common	Uncommon	Very rare
Blood and lymphatic system disorders			Thrombocytopenia
Immune system disorders			Allergic reaction
Metabolism and nutrition disorders			Hyperglycemia
Psychiatric disorders		Insomnia, mood changes	
Nervous system disorders	Dizziness, headache, somnolence	Hypoesthesia, paresthesia, tremor, taste perversion, syncope	Peripheral neuropathy
Eye disorders		Visual disturbances	
Ear and labyrinth disorders		Tinnitus	
Cardiac disorders	Palpitations		Acute myocardial infarction, arrhythmia, ventricular tachycardia and atrial fibrillation

Vascular disorders	Flushing	Hypotension	Vasculitis
Respiratory, thoracic and mediastinal disorders		Dyspnea, rhinitis	Coughing
Gastrointestinal disorders	Nausea, abdominal pain	Dyspepsia, vomiting, altered bowel habits, dry mouth	Pancreatitis, gastritis, gingival hyperplasia
Hepatobiliary disorders			Hepatitis, jaundice and elevated liver enzymes (in most cases, consistent with cholestasis)
Skin and subcutaneous disorders		Urticaria, pruritus, purpura, increased sweating, skin discoloration, alopecia	Angioedema, erythema multiforme, urticaria
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	Fatigue, edema	Chest pain, asthenia, general malaise, nonspecific pain	
Investigations		Weight gain, weight loss	

In the clinical trials 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 postmarketing 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
Irbesartan monotherapy		
General disorders and administration site conditions		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
Injury, poisoning and procedural complications		fall
Amlodipine Monotherapy		
General disorders and administration site conditions	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
Irbesartan/amlodipine Fixed-dose Combination		
General disorders and administration site conditions	peripheral edema, edema	asthenia
Ear and labyrinth disorders		vertigo
Cardiac disorders	palpitations	sinus bradycardia
Nervous system disorders	dizziness, headache, somnolence	paresthesia
Reproductive system and breast disorders		erectile dysfunction
Respiratory, thoracic and mediastinal disorders		cough
Vascular disorders	postural hypotension	hypotension

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

INTERACTIONS WITH OTHER DRUGS AND OTHER FORMS OF INTERACTION:

For the 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 performed with Aprovasc® and other medicinal products.

Irbesartan: Based on in vitro data, no interactions would be expected to occur with drugs for which metabolism depends on cytochrome P450 isoenzymes CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2D6, CYP2E1 or CYP3A4.

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

Co-administration with nifedipine or hydrochlorothiazide has no effect on the pharmacokinetic profile of irbesartan.

Irbesartan has no effect on the pharmacokinetics of simvastatin (metabolized by CYP3A4) or digoxin (substrate of P-glycoprotein efflux transporter).

Based on experience with the use of other drugs with an effect on the renin-angiotensin system, concomitant use of potassium-sparing diuretics, potassium supplements, or salt substitutes containing potassium may increase serum potassium levels.

Use of Aprovasc® concomitantly with medicinal products containing aliskiren is contraindicated in patients with diabetes mellitus or moderate to severe renal insufficiency (glomerular filtration rate [GFR] <60 mL/min/1.73 m2), and is not recommended in other patients.

Angiotensin-converting enzyme (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.

In elderly patients, volume-depleted patients (including those treated with diruetics), or in patients with impaired renal function, co-administration of irbesartan with NSAIDs, including selective COX-2 inhibitors, or with angiotenisin II receptor antagonists, including irbesartan, can cause deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Renal function should be monitored periodically in patients receiving occasional treatment with irbesartan and NSAIDs. The antihypertensive effect of angiotenisin II receptor antagonists, including irbesartan, may be attenuated by NSAIDs including selective COX-2 inhibitors.

Amlodipine: Amlodipine has been safely co-administered with thiazide diuretics, beta blockers, alpha blockers, ACE inhibitors, long-acting nitrates, sublingual glyceryl trinitrate, NSAIDs, antibiotics, and oral hypoglycemic drugs.

Data from *in vitro* studies with human plasma indicate that amlodipine has no effect on the protein binding of the medicinal products studied (digoxin, phenytoin, warfarin or indomethacin).

- Cimetidine: Co-administration of amlodipine with cimetidine had no effect on the pharmacokinetic profile of amlodipine.

- Grapefruit juice: Co-administration of 240 mL of grapefruit juice with a single 10 mg oral dose of amlodipine in 20 healthy subjects had no significant effect on the pharmacokinetics of amlodipine.

- Aluminum/magnesium (antacids): Concomitant administration of an antacid containing aluminum/magnesium with a single dose of amlodipine had no significant effect on the pharmacokinetic profile of amlodipine.

- Sildenafil: When amlodipine and sildenafil were used in combination, each agent independently exerted a blood pressure lowering effect.

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

- Digoxin: Co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in healthy subjects.

- Warfarin: Co-administration of amlodipine did not significantly change the effect of warfarin on prothrombin time.

- Cyclosporine: Pharmacokinetic studies with cyclosporine have demonstrated that amlodipine has no significant effect on cyclosporine pharmacokinetics.

- Lithium: Increased serum lithium concentrations and lithium toxicity have been reported with concomitant use of irbesartan requiring monitoring of lithium levels during co-administration.

Laboratory test abnormalities:

No clinically significant changes in laboratory test parameters were observed in controlled clinical studies with irbesartan in hypertensive patients. No special monitoring of laboratory parameters is required in patients with essential hypertension receiving treatment with irbesartan.

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

Irbesartan:

No carcinogenic evidence was observed with administration of irbesartan at doses of up to 500/1000 mg/kg/day in rats (male/female, respectively) and 1000 mg/kg/day in mice for 2 years. These doses provided a systemic exposure 4-25 times (rats) and 4-6 times (mice) the exposure in humans receiving 300 mg/day.

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

Fertility and reproductive performance were not affected in studies of male and female rats, even at doses causing some parental toxicity (up to 650 mg/kg/day). No significant effects on the number of corpora luteal

implants, or live fetuses were observed. Irbesartan had no effect on survival, development, or reproduction of 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 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 (similar to the maximum recommended human dose of 10 mg on a mg/m2 basis for mice, and about twice* this maximum dose for rats) was close to the maximum tolerated dose for mice but not for rats.

Mutagenesis: Mutagenesis studies revealed no amlodipine-related effects 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 for 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m2 basis).

* Based on a 50 kg patient.

SIGNS AND MANAGEMENT OF OVERDOSAGE OR ACCIDENTAL INTAKE:

Experience in adults exposed to doses of up to 900 mg/day irbesartan for 8 weeks revealed no toxicity. No specific information is available on the treatment of overdose with irbesartan. Available data for amlodipine suggest that overdose could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension and shock with fatal outcome have been reported. The patient should be closely monitored and symptomatic and supportive treatment administered.

Suggested measures include gastric lavage. Administration of activated charcoal to healthy subjects immediately or up to two hours after ingestion of amlodipine 10 mg has been shown to significantly decrease amlodipine absorption.
As amlodipine is highly protein bound and irbesartan is not removed from the body by hemodialysis, hemodialysis does not appear to be useful.

If massive overdose should occur, active cardiac and respiratory monitoring should be initiated. Frequent blood pressure measurement is essential. Clinically significant hypotension due to amlodipine overdose calls for active cardiovascular support including elevation of the extremities and attention to circulating fluid volume and urine output. A vasoconstrictor may be helpful in restoring 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
Irbesartan 150 mg and amlodipine 10 mg
Irbesartan 300 mg and amlodipine 5 mg
Irbesartan 300mg 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 de Ocoyoacac,
C. P. 52740 Ocoyoacac, Edo. de México

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