APROVASC® Abridged Prescribing Information:

1. NAME & PRESENTATION: APROVASC 150 mg / 5 mg – 150 mg / 10 - 300 mg / 5 mg and 300 mg / 10 mg tablets,

Each tablet contains:
Irbesartan 150 mg 150 mg 300 mg 300 mg
Amlodipine
besylate,
Equivalent to
amlodipine
5 mg 10 mg 5 mg 10 mg
Excipient qs 1 tablet 1 tablet 1 tablet 1 tablet

2. 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.

3. DOSAGE & 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.

4. SPECIAL POPULATION: 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

4. CONTRA-INDICATIONS: 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 Section 4.6 Fertility, 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.

WARNINGS & PRECAUTIONS: 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 and in

those undergoing intensive diuretic treatment and/or salt restriction, or on hemodialysis. Volume

and/or and sodium depletion should be corrected before therapy with APROVASC® is initiated

or the lowest possible starting dose should be considered.

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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 to and death of the developing fetus. Thus, as for any drug that acts directly on the renin-angiotensin-aldosterone system, APROVASC® should not be used during pregnancy. If pregnancy is detected during treatment, 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 of heart failure compared to placebo (see Pharmacodynamics).

Hepatic impairment: As with other calcium antagonists, amlodipine half-life is prolonged in patients with impaired liver function and no dosage recommendations have been established in this population. APROVASC® should therefore be administered with caution in these patients.

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

6. INTERACTIONS: 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.

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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.

7. 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.

Lactating mothers: APROVASC® is contraindicated during lactation

9. ADVERSE REACTIONS: **Very common**: 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 post marketing experience with irbesartan are categorized below according to system organ class and frequency For amlodipine :Adverse events that have been reported in amlodipine trials are categorized below according to system organ class and frequency. 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.

10.Overdose: 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.

11.Pharmacodynamics: 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

12. MARKETING AUTHORIZATION HOLDER: 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 Abbreviated Prescribing Information based on the EU SmPC as of Aug 2015 . Always refer to the full Summary of Product Characteristics (SmPC) before prescribing.