APROVASC® 150 mg/ 5 mg
APROVASC® 150 mg/ 10 mg
APROVASC® 300 mg/ 5 mg
APROVASC® 300 mg/ 10 mg

Irbesartan / amlodipine besylate
Film coated tablets

SANOFI

1. TRADE NAME:
APROVASC
2. GENERIC NAME:
Irbesartan / Amlodipine besylate
3. PHARMACEUTICAL DOSAGE FORM AND COMPOSITION:
FILM COATED TABLETS
FORMULATION:

Each film coated tablet contains				
Irbesartan	150 mg	150 mg	300 mg	300 mg
Amlodipine besylate equivalent to amlodipine	5 mg	10 mg	5 mg	10 mg
microcrystalline cellulose, croscarmellose sodium, hydroxypropyl methylcellulose, colloidal silicon dioxide, magnesium stearate, polyethylene glycol, titanium dioxide, red iron oxide (Aprovasc® 150mg/10mg), yellow iron oxide (Aprovasc® 300mg/5mg) qs	1 tablet	1 tablet	1 tablet	1 tablet

4. THERAPEUTIC INDICATIONS:
Treatment of essential hypertension.
APROVASC is indicated in patients whose blood pressure is not adequately controlled on irbesartan or amlodipine monotherapy.
5. CONTRAINDICATIONS:
Due to the presence of both irbesartan and amlodipine, APROVASC is contraindicated in:
- hypersensitivity to either or both of the active substances or to any of the formulation components
- hypersensitivity to dihydropyridines
- cardiogenic shock, clinically significant aortic stenosis, unstable angina (excluding Prinzmetal's angina)
- pregnancy and lactation (see Warnings and section 8, Restrictions during Pregnancy and Lactation).

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 signifi- cant 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.
6. 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.
7. RESTRICTIONS DURING 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 therapy with APROVASC, treatment shall be discontinued as soon as possible (see section 6, Contraindications and Warnings).
Lactating mothers: APROVASC is contraindicated during lactation (see section 6, Contraindications).
8. SIDE-EFFECTS AND ADVERSE REACTIONS:
ADVERSE EVENTS: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
Irbesartan has been evaluated for safety in approximately 5000 subjects in clinical studies, including 1300 hypertensive patients treated for over 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. The incidence of adverse events was not related to age, gender or race.
In placebo-controlled clinical studies, including 1965 irbesartan-treated patients (usual duration of treatment 1 to 3 months), treatment discontinuation due to any clinical or laboratory adverse event were 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 irbesartan trials or postmarketing are categorized below according to system organ class and frequency (see table 1).
The frequency of adverse events is defined using the following convention: Very common: (≥ 1/10); common: (≥ 1/100 and < 1/10); uncommon: (≥ 1/1,000 and < 1/100); rare: (≥ 1/10,000 and < 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 1 - Adverse Events Reported in Irbesartan Clinical Trials or Postmarketing Reports

	Common(a)	Uncommon(b)	Unknown
Immune system disorders			Hyperesensitivity reactions
Metabolism and nutrition disorders			Hyperkalemia
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
Musculoskeletal and connective tissue disorders			Myalgia
Renal and urinary disorders			Impaired renal function including isolated cases of renal failure in patients at risk
Reproductive system and breast disorders		Sexual dysfunction	
General disorders and administration site conditions	Fatigue, edema	Chest pain	Asthenia

a Include all adverse events, probably or possibly related, or of uncertain relationship to therapy, whatever their incidence in the placebo-treated patients
b include all adverse events, probably or possibly related, or of uncertain relationship to therapy, occurring with a frequency of 0.5% to <1% and at similar or slightly increased incidence in irbesartan-treated patients than in placebotreated patients (none of them were statistically significantly different 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 2).
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 2 - 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		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 hepatic enzyme elevations (mostly consistent with cholestasis)
Skin and subcutaneous disorders		Pruritus, rash, 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, malaise, pain	
Investigations		weight increase, weight decrease	

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 the earlier monotherapy clinical trials and postmarketing reports. The most frequently reported adverse event was peripheral edema, mainly associated with amlodipine.
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 3 - 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 Combination		
General disorders and administration site conditions	**peripheral edema, edema**	**asthenia**
Ear and labyrinth disorders		**vertigo**
Cardiac disorders	**palpitations**	**sinus bradvacardia**
Nervous system disorders	**dizzines, headache, somnolence**	**parathesia**
Reproductive system and breast disorders		**erectile dysfunction**
Respiratory, thoracic and mediastinal disorders	**sinus bradvacardia**	**cough**
Vascular disorders	**orthostatic hypotension**	**hypotension**
Gastrointestinal disorders	**gingival swelling**	**nausea, upper abdominal pain, constipation**
Renal and urinary disorders	**proteinuria**	**azotemia, hypercreatinemia**

Table 3 - 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/amlodipine Fixed Combination		
Metabolism and nutrition disorders		**hyperkalemia**
Musculoskeletal and connective tissue disorders		**joint stiffness, arthralgia, myalgia**

9. INTERACTIONS WITH OTHER DRUGS AND OTHER FORMS OF INTERACTION:
For irbesartan and amlodipine combination: Based on a pharmacokinetic study where irbesartan and amlodipine were given 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 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 pharmacodynamic interactions were observed when irbesartan was co-administered with warfarin (metabolized by CYP2C9).
The pharmacokinetic parameters of irbesartan are not affected by co-administeration with nifedipine or hydrochlorothiazide.
Irbesartan does not affect the pharmacokinetics of simvastatin (metabolized by CYP3A4) or digoxin (substrate of P-glycoprotein efflux transporter).
Based on experience with the use of other drugs that a ect the renin-angiotensin system, concomitant use of potassium-sparing diuretics, potassium supplements, or salt substitutes containing potassium may increase serum potassium levels.
Amlodipine: Amlodipine has been safely co-administered with thiazide diuretics, beta blockers, alpha blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual glyceryl trinitrate, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.
Data from in vitro studies with human plasma indicate that amlodipine has no effect on the protein binding of studied medicines (digoxin, phenytoin, warfarin or indomethacin).
• Cimetidine: Co-administration of amlodipine with cimetidina did not alter the pharmacokinetics of amlodipine.
• Grapefruit juice: Co-administration of 240 mL of grapefruit juice with a single oral dose of amlodipine 10 mg in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine.
• Sildenafil: When amlodipine and sildenafil were used in combination, each agent independently exerted its own 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 volunteers.
• Warfarin: Co-administration of amlodipine did not change warfarin prothrombin response time.
• Cyclosporine: Pharmacokinetic studies with cyclosporine have demonstrated that amlodipine does not significantly alter the pharmacokinetics of cyclosporine.
10. PRECAUTIONS RELATED TO CARCINOGENESIS, MUTAGENESIS AND 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 up to 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 inducement 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 lutea, implants, or live fetuses were observed. Irbesartan did not affect survival, development, or reproduction of offspring.
Transient toxic effects (increased renal pelvic cavitation, hydroureter or subcutaneous edema) in rat fetuses were observed 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 teratogenic effects were observed in the rat or rabbit.
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/m^2 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/m^2 basis).
* Based on a 50 kg patient.
11. DOSAGE AND 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 noadequately controlled on monotherapy with irbesartan or amlodipine or for continuation of therapy for patients receiving irbesartan and amlodipine as separate tablets. Dose should be individualized based on response to therapy with individual components and antihypertensive response required. The maximum recommended dose with APROVASC is 300 mg/10 mg per day
Therapy should be adjusted according to blood pressure response.
Pediatric patients: The safety and efficacy of APROVASC has not been established.
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 degree).
Patients with impaired hepatic function: Due to the presence of amlodipine, APROVASC should be administered with caution (see section 6, Warnings).
For oral administration
12. 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 overdosage with irbesartan. Available data for amlodipine suggest that gross overdosage could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported. The patient should be closely monitored, and the treatment should be symptomatic and supportive.
Suggested measures include gastric lavage. Administration of activated charcoal to healthy volunteers 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 is not likely to be of benefit.
If massive overdose should occur, initiate active cardiac and respiratory monitoring. Frequent blood pressure measurements are essential. Clinically significant hypotension due to amlodipine overdosage calls for active cardiovascular support including elevation of 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.
13. MARKETING PRESENTATIONS:
Cardboard box with 14 or 28 film coated tablets of 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 in blister packs.
Not all pack sizes may be marketed in your country.
14. STORAGE CONDITIONS:
Store at room temperature below 30°C, protected from moisture.
15. SPECIAL WARNINGS:
Exclusive literature for physicians
Keep out of the reach and sight of children
Prescription only medicine.
Do not use during pregnancy and breastfeeding.

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BPI
Dbayeh - Lebanon

This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament
- The doctor and the pharmacist are experts in medicine, its benefits and risks
- Do not by yourself interrupt the period of treatment prescribed for you
- Do not repeat the same prescription without consulting your doctor
- Medicament: keep out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

P1L30/2