IRSTRAN® FILM COATED TABLET

Ingredient(s):
Each film coated tablet contains:
Irstran Film Coated Tablet 150mg
Irbesartan 150mg
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Irstran Film Coated Tablet 300mg
Irbesartan 300mg

Pharmacodynamics:
Pharmacotherapeutic group: Angiotensin II antagonists, ATC code : C09CA04
Irbesartan is a nonpeptide competitive angiotensin II antagonist that selectively blocks the binding of angiotensin II to the AT 1 receptor. In the renin-angiotensin system, angiotensin I is converted by angiotensin-converting enzyme (ACE) to form angiotensin II. Angiotensin II stimulates the adrenal cortex to synthesize and secrete aldosterone, which decreases the excretion of sodium and increases the excretion of potassium. Angiotensin II also acts as a vasoconstrictor in vascular smooth muscle. Irbesartan, by blocking the binding of angiotensin II to the AT 1 receptor, promotes vasodilation and decreases the effects of aldosterone. The negative feedback regulation of angiotensin II on renin secretion also is inhibited, but the resulting rise in plasma renin concentrations and consequent rise in angiotensin II plasma concentrations do not counteract the blood pressure-lowering effect that occurs.

Pharmacokinetics:
Absorption
Irbesartan is rapidly absorbed from the gastrointestinal tract with an oral bioavailability of 60 to 80%. Peak plasma concentrations of Irbesartan occur 1.5 to 2 hours after an oral dose. Irbesartan may be dosed without regards to meals.

Distribution
Irbesartan is about 96% bound to plasma proteins. The volume of distribution is 53-93 litres.

Metabolism
Irbesartan is metabolised in the liver via glucuronide conjugation and oxidation, primarily by the cytochrome P450 isoenzyme CYP2C9, to inactive metabolites. The major circulating metabolite is Irbesartan glucuronide (approximately 6%).

Elimination
It is excreted as unchanged drug and metabolites in the bile and in urine. The terminal elimination half-life is about 11 to 15 hours. The total body clearance is 157-176 ml/min.

Indication:
1. Treatment of essential hypertension.
2. Treatment of renal disease in patients with hypertension and type 2 diabetes mellitus as part of an antihypertensive drug regimen.

Dosage and Administration:
The usual recommended initial and maintenance dose is 150 mg once daily, with or without food.

Irbesartan at a dose of 150 mg once daily generally provides a better 24 hour blood pressure control than 75 mg. However, initiation of therapy with 75 mg could be considered, particularly in haemodialysed patients and in the elderly over 75 years.

In patients insufficiently controlled with 150 mg once daily, the dose of Irbesartan can be increased to 300 mg, or other anti-hypertensive agents can be added. In particular, the addition of a diuretic such as hydrochlorothiazide has been shown to have an additive effect with Irbesartan.

In hypertensive type 2 diabetic patients, therapy should be initiated at 150 mg Irbesartan once daily and titrated up to 300 mg once daily as the preferred maintenance dose for treatment of renal disease. The demonstration of renal benefit of Irbesartan in hypertensive type 2 diabetic patients is based on studies where Irbesartan was used in addition to other antihypertensive agents, as needed, to reach target blood pressure.

Renal impairment: No dosage adjustment is necessary in patients with impaired renal function. A lower starting dose (75 mg) should be considered for patients undergoing haemodialysis.

Intravascular volume depletion: Volume and/or sodium depletion should be corrected prior to administration of Irbesartan.

Hepatic impairment: No dosage adjustment is necessary in patients with mild to moderate hepatic impairment. There is no clinical experience in patients with severe hepatic impairment.

Elderly patients: Although consideration should be given to initiating therapy with 75 mg in patients over 75 years of age, dosage adjustment is not usually necessary for the elderly.

Children: Safety and efficacy of Irbesartan have not been established in children.

Route of Administration:
To be taken orally.

Contraindication:

USE IN PREGNANCY
When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, Irbesartan should be discontinued as soon as possible.

1. Hypersensitivity to the active substance or to any of the excipients.
2. Second and third trimesters of pregnancy.
3. Do not administer Irbesartan with angiotensin-converting enzyme inhibitors (ACEIs) in patients with diabetic nephropathy.
4. The concomitant use of Irbersartan with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (glomerular filtration rate (GFR) <60ml/min/1.73 m²).

Precaution(s) / Warning:
1. Intravascular volume depletion: symptomatic hypotension, especially after the first dose, may occur in patients who are volume and/or sodium depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Such conditions should be corrected before the administration of this product.
2. Renovascular hypertension: there is an increased risk of severe hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with medicinal products that affect the renin-angiotensin-aldosterone system. A similar effect should be anticipated with angiotensin-II receptor antagonists.
3. Renal impairment and kidney transplantation: when Irbesartan is used in patients with impaired renal function, a periodic monitoring of potassium and creatinine serum levels is recommended. There is no experience regarding the administration of irbesartan in patients with recent kidney transplantation.
4. Hypertensive patients with type 2 diabetes and renal disease: the effects of irbesartan both on renal and cardiovascular events were not uniform across all subgroups. In particular, they appeared less favourable in women and non-white subjects.
5. Dual blockade of the renin-angiotensin-aldosterone system (RAAS):
   There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended. If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.
6. Hyperkalaemia: as with other medicinal products that affect the renin-angiotensin-aldosterone system, hyperkalaemia may occur during the treatment with this product, especially in the presence of renal impairment, overt proteinuria due to diabetic renal disease, and/or heart failure. Close monitoring of serum potassium in patients at risk is recommended.
7. Lithium: the combination of lithium and Irbesartan is not recommended.
8. Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy: as with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.
9. Primary aldosteronism: patients with primary aldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of this product is not recommended.
10. General: in patients whose vascular tone and renal function depend predominantly on the activity of the system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with angiotensin converting enzyme inhibitors or angiotensin-II receptor antagonists that affect this system has been associated with acute hypotension, azotaemia, oliguria, or rarely acute renal failure. As with any antihypertensive agent, excessive blood pressure decrease in patients with ischaemic cardiopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke.
    As observed for angiotensin converting enzyme inhibitors, irbesartan and the other angiotensin antagonists are apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population.
11. Pregnancy: Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started.
12. Lactose: this medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
13. Paediatric population: the current data are insufficient to support an extension of the use in children.
14. Hypoglycemia: Irbesartan may induce hypoglycemia, particularly in patients treated for diabetes. Therefore, dose adjustment of antidiabetic treatment such as repaglinide or insulin may be required (see Undesirable effects).
15. Effects on ability to drive and use machines: Based on its pharmacodynamic properties, irbesartan is unlikely to affect the ability to drive and use machines. When driving vehicles or operating machines, it should be taken into account that dizziness or weariness may occur during treatment.

Interaction with Other Medicaments:
1. Diuretics and other antihypertensive agents: other antihypertensive agents may increase the hypotensive effects of irbesartan; however this product is safely administered with other antihypertensive agents, such as beta-blockers, long-acting calcium channel blockers, and thiazide diuretics. Prior treatment with high dose diuretics may result in volume depletion and a risk of hypotension when initiating therapy with this product.
2. Aliskiren-containing products and ACE-inhibitors: dual blockade of the renin-angiotensin-aldosterone system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent.
3. Potassium supplements and potassium-sparing diuretics: concomitant use of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicinal products that may increase serum potassium levels

L
260mm
(±2mm)

W
220mm (±2mm)

Item Code	: 2XXXXX - XX
PM Code	: Ins.P. IST&IST3 (S)
Measurement(mm) ± 2mm	: 260 (L) x 220 (W)
Colour of Artwork	: K
Source of Artwork	: MAC 3 / CC
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Item Code	: 2XXXXX - XX
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(e.g. heparin) may lead to increases in serum potassium and is, therefore, not recommended.

4. Lithium: reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors. Similar effects have been very rarely reported with irbesartan so far. Therefore, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended.

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

6. Additional information on irbesartan interactions: Irbesartan is mainly metabolised by CYP2C9 and to a lesser extent by glucuronidation. No significant pharmacokinetic or pharmacodynamic interactions were observed when irbesartan was coadministered with warfarin, a medicinal product metabolised by CYP2C9. The effects of CYP2C9 inducers such as rifampicin on the pharmacokinetic of irbesartan have not been evaluated. The pharmacokinetic of digoxin was not altered by coadministration of irbesartan.

7. Angiotensin-converting enzyme inhibitors (ACEIs): the use of irbesartan in combination with an ACEI is contraindicated in patients with diabetic nephropathy and is not recommended in other patients.

8. Repaglinide: Irbesartan has the potential to inhibit OATP1B1. In a clinical study, it was reported that irbesartan increased the Cmax and AUC of repaglinide (substrate of OATP1B1) by 1.8-fold and 1.3-fold, respectively, when administered 1 hour before repaglinide. In another study, no relevant pharmacokinetic interaction was reported when the two drugs were coadministered. Therefore, dose adjustment of antidiabetic treatment such as repaglinide may be required (see Precaution(s) / Warning).

Pregnancy and Lactation:
Pregnancy

The use of AIIRAs is not recommended during the first trimester of pregnancy.
The use of AIIRAs is contraindicated during the second and third trimesters of pregnancy.

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with Angiotensin II Receptor Antagonists (AIIRAs), similar risks may exist for this class of drugs. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to AIIRA therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia).

Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Infants whose mothers have taken AIIRAs should be closely observed for hypotension.

Lactation
Because no information is available regarding the use of irbesartan during breast-feeding, irbesartan is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

It is unknown whether irbesartan or its metabolites are excreted in human milk.

Fertility
Irbesartan had no effect upon fertility of treated rats and their offspring up to the dose levels inducing the first signs of parental toxicity.

Side Effects:
The frequency of adverse reactions listed below 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). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness

Blood and lymphatic system disorders:
Not known : thrombocytopenia
Immune system disorders:
Not known : hypersensitivity reactions such as angioedema, rash, urticaria
Metabolism and nutrition disorders:
Not known : hyperkalaemia
Nervous system disorders:
Common : dizziness, orthostatic dizziness
Not known : vertigo, headache
Ear and labyrinth disorder:
Not known : tinnitus
Cardiac disorders:
Uncommon : tachycardia
Vascular disorders:
Common : orthostatic hypotension
Uncommon : flushing
Respiratory, thoracic and mediastinal disorders:
Uncommon : cough
Gastrointestinal disorders:
Common : nausea/vomiting
Uncommon : diarrhoea, dyspepsia/heartburn
Not known : dysgeusia
Hepatobiliary disorders:
Uncommon : jaundice
Not known : hepatitis, abnormal liver function
Skin and subcutaneous tissue disorders:
Not known : leukocytoclastic vasculitis
Musculoskeletal and connective tissue disorders:
Common : musculoskeletal pain
Not known : arthralgia, myalgia (in some cases associated with increased plasma creatine kinase levels), muscle cramps
Renal and urinary disorders:
Not known : impaired renal function including cases of renal failure in patients at risk
Reproductive system and breast disorders:
Uncommon : sexual dysfunction
General disorders and administration site conditions:
Common : fatigue
Uncommon : chest pain

Investigations:
Very Common: Hyperkalaemia occurred more often in diabetic patients treated with irbesartan than with placebo. In diabetic hypertensive patients with microalbuminuria and normal renal function, hyperkalaemia (≥ 5.5 mEq/L) occurred in 29.4% of the patients in the irbesartan 300 mg group and 22% of the patients in the placebo group. In diabetic hypertensive patients with chronic renal insufficiency and overt proteinuria, hyperkalaemia (≥ 5.5 mEq/L) occurred in 46.3% of the patients in the irbesartan group and 26.3% of the patients in the placebo group.
Common: Significant increases in plasma creatine kinase were commonly observed (1.7%) in irbesartan treated subjects. None of these increases were associated with identifiable clinical musculoskeletal events. In 1.7% of hypertensive patients with advanced diabetic renal disease treated with irbesartan, a decrease in haemoglobin*, which was not clinically significant, has been observed

Symptoms and Treatment of Overdose:
Symptoms
Mild hypotension and tachycardia, hypokalemia, asymptomatic hypoglycemia, muscle cramps and dizziness have been reported. Bradycardia might also occur from overdose.
Treatment
The patient should be closely monitored, and the treatment should be symptomatic and supportive. Activated charcoal may be useful in the treatment of overdose. As Irbesartan is highly protein bound; hemodialysis is unlikely to be of any benefit.

Storage Condition:
Store at temperature below 30ºC.

Shelf Life:
2 years.

List of Excipients:
Colloidal Silicon Dioxide
Croscarmellose Sodium
Lactose Monohydrate
Hydroxypropyl Methylcellulose
Microcrystalline Cellulose
Magnesium Stearate
Ethanol
Purified Water
Opadry II White

Product Description and Packing(s):
Irstran Film Coated Tablet 150mg
A white film coated elliptical tablet, one side impressed with `150'. (150)
Blister packing of 10's x 3, 10's x 6 and 10's x 10.
Irstran Film Coated Tablet 300mg
A white film coated elliptical tablet, one side impressed with `300'. (300)
Blister packing of 10's x 3, 10's x 6 and 10's x 10.
Not all presentation may be available locally.

Y. S. P.®
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