



CRUZORTABLET 300 MG

CRUZOR TABLET 150 MG

COMPOSITION

Cruzor Tablet 150mg

Each film coated tablet contains 150mg of Irbesartan

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DESCRIPTION

Cruzor Tablet 150mg

12.5 mm length, white to off-white, oval-shaped film-coated tablet with Pharmaniaga icon on one side and plain on the other side.

Cruzor Tablet 300mg

15.5 mm length, white to off-white, oval-shaped film-coated tablet with Pharmaniaga icon on one side and plain on the other side.

PHARMACODYNAMICS

Irbesartan is a potent, orally active, selective angiotensin II receptor (type AT 1) antagonist that 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. Irbesartan does not inhibit ACE (kinase II), an enzyme which generates angiotensin II and also degrades bradykinin into inactive metabolites. Irbesartan does not require metabolic activation for its activity.

PHARMACOKINETICS

Absorption and distribution

After oral administration, irbesartan is well absorbed: studies of absolute bioavailability gave values of approximately 60-80%. Concomitant food intake does not significantly influence the bioavailability of irbesartan. Plasma protein binding is approximately 96%, with negligible binding to cellular blood

components. The volume of distribution is 53 - 93 litres. Following oral administration of 14C irbesartan, 80-85% of the circulating plasma radioactivity is attributable to unchanged irbesartan. Irbesartan is metabolised by the liver via glucuronide conjugation and oxidation. The major circulating metabolite is irbesartan glucuronide (approximately 6%). Irbesartan is primarily oxidised by the cytochrome P450 enzyme CYP2C9; isoenzyme CYP3A4 has negligible effect.

Irbesartan exhibits linear and dose proportional pharmacokinetics over the dose range of 10 to 600 mg. A less than proportional increase in oral absorption at doses beyond 600 mg (twice the maximal recommended dose) was observed; the mechanism for this is unknown. Peak plasma concentrations are attained at 1.5 - 2 hours after oral administration. The total body and renal clearance are 157 - 176 and 3 - 3.5 ml/min, respectively. The terminal elimination half-life of irbesartan is 11 - 15 hours. Steady-state plasma concentrations are attained within 3 days after initiation of a once-daily dosing regimen. Limited accumulation of irbesartan (< 20%) is observed in plasma upon repeated once-daily dosing.

Metabolism and elimination

Irbesartan and its metabolites are eliminated by both biliary and renal pathways. After oral administration of 14C irbesartan, about 20% of the radioactivity is recovered in the urine, and the remainder in the faeces. Less than 2% of the dose is excreted in the urine as unchanged irbesartan.

Paediatric population

Cmax, AUC and clearance rates were comparable to those observed in adult patients receiving 150 mg irbesartan daily. A limited accumulation of irbesartan (18%) in plasma was observed upon repeated once daily dosing.

Renal impairment

In patients with renal impairment or those undergoing haemodialysis, the pharmacokinetic parameters of irbesartan are not significantly altered. Irbesartan is not removed by haemodialysis.

Hepatic impairment

In patients with mild to moderate cirrhosis, the pharmacokinetic parameters of irbesartan are not significantly altered.

Studies have not been performed in patients with severe hepatic impairment.

INDICATION

Treatment of essential hypertension.

Treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria (>300 mg/day) in patients with type 2 diabetes and hypertension.

In this population, Irbesartan reduces the rate of progression of nephropathy as measured by the occurrence of doubling of serum creatinine or end-stage renal disease (need for dialysis or renal transplantation).

RECOMMENDED DOSAGE

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 hours 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 antihypertensive 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.

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

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.

Paediatric patients: Irbesartan is not recommended for use in children and adolescents due to insufficient data on safety and efficacy.

Cruzor Tablet 150mg and Cruzor Tablet 300mg are not able to deliver all approved dose regimens of Irbesartan; other approved dosage forms and strengths of Irbesartan should be used in such cases. If a lower starting dose is considered necessary, the 150 mg tablet not being breakable, alternative therapy should be considered.

ROUTE OF ADMINISTRATION

Oral

CONTRAINDICATIONS

Hypersensitivity to the active substance, or to any of the excipients.

Second and third trimesters of pregnancy.

The concomitant use of Irbesartan with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (glomerular filtration rate (GFR) < 60ml/min/1.73m²).

WARNINGS AND PRECAUTIONS

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 Irbesartan.

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. While this is not documented with Irbesartan, a similar effect should be anticipated with angiotensin-II receptor antagonists.

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 a recent kidney transplantation.

Hypertensive patients with type 2 diabetes and renal disease: The effects of Irbesartan both on renal and cardiovascular events were not uniform in patients with advanced renal disease. In particular, they appeared less favourable in women and non-white patients.

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.

Hyperkalaemia:As with other medicinal products that affect the renin-angiotensin-aldosterone system, hyperkalaemia may occur during the treatment with Irbesartan, 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.

Lithium: The combination of lithium and Irbesartan is not recommended.

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.

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 Irbesartan is not recommended.

General: In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone 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.

Use in black patients: 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.

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.

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.

Paediatric population: The current data are insufficient to support an extension of the use in children until further data become available.

EFFECTS ON THE ABILITY TO DRIVE AND USE MACHINES

Based on its pharmacodynamic properties, Irbesartan is unlikely to affect this ability. When driving vehicles or operating machines, it should be taken into account that dizziness or weariness may occur during treatment.

INTERACTIONS WITH OTHER MEDICAMENTS

Diuretics and other antihypertensive agents: Other antihypertensive agents may increase the hypotensive effects of Irbesartan; however Irbesartan has been 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 Irbesartan.

Aliskiren-containing products and ACE-inhibitors: It has been shown that dual blockade of the reninangiotensin-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.

Potassium supplements and potassium-sparing diuretics: Based on experience with the use of other medicinal products that affect the renin-angiotensin system, concomitant use of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicinal products that may increase serum potassium levels (e.g. heparin) may lead to increases in serum potassium and is, therefore, not recommended.

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.

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 (> 3 g/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.

Additional information on Irbesartan interactions: The pharmacokinetic of Irbesartan is not affected by hydrochlorothiazide. 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.

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.

Breast-feeding:

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. Available pharmacodynamic/ toxicological data in rats have shown excretion of irbesartan or its metabolites in milk.

ADVERSE EFFECTS

Immune system disorders:

Not known: Hypersensitivity reactions such as angioedema, rash, urticaria, anaphylactic reaction, anaphylactic shock

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

Blood and Lymphatic System Disorders:

Not Known: Thrombocytopenia

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

Common: Significant increases in plasma creatine kinase

Paediatric population:

Headache, hypotension, dizziness, cough, increased creatinine and elevated CK values.

OVERDOSE AND TREATMENT

Symptoms

Experience in adults exposed to doses of up to 900 mg/day for 8 weeks revealed no toxicity. The most likely manifestations of overdose are expected to be hypotension and tachycardia; bradycardia might also occur from overdose.

Treatment:

No specific information is available on the treatment of overdose with Irbesartan. The patient should be closely monitored, and the treatment should be symptomatic and supportive. Suggested measures include induction of emesis and/or gastric lavage. Activated charcoal may be useful in the treatment of overdose. Irbesartan is not removed by haemodialysis.

STORAGE CONDITION

Store below 30°C.

Store in the original package.

SHELF LIFE

Product should not be used beyond the expiry date imprinted on the product packaging.

DOSAGE FORMS AND PACKAGING AVAILABLE

In boxes of 30 tablets (3 blisters x 10 tablets).

PRODUCT REGISTRATION HOLDER/MANUFACTURER:

PHARMANIAGA MANUFACTURING BERHAD(60016-D)

11A, Jalan P/1, Kawasan Perusahaan Bangi,

43650 Bandar Baru Bangi, Selangor Darul Ehsan, Malaysia

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