Ibecard® - IPS

Irbesartan

FORMS AND PRESENTATION
Ibecard® 150 - IPS: Film coated tablets: Box of 30.
Ibecard® 300 - IPS: Film coated tablets: Box of 30.

COMPOSITION
Ibecard® 150 - IPS: Each film coated tablet contains Irbesartan 150mg.
Ibecard® 300- IPS: Each film coated tablet contains Irbesartan 300mg.
Excipients: Lactose, Microcrystalline Cellulose, Povidone, Sodium Starch Glycolate, Magnesium Stearate, Hypromellose, Titanium Dioxide, Talc, Polyethylene Glycol.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties
Therapeutic class: Agents acting on the renin-angiotensin system.
ATC code: C09CA04.
Irbesartan is a potent, orally active, selective angiotensin-II receptor (type AT_1) antagonist. It is expected to block all actions of angiotensin-II mediated by the AT_1 receptor, regardless of the source or route of synthesis of angiotensin-II. The selective antagonism of the angiotensin-II (AT_1) receptors results in increases in plasma renin levels and angiotensin-II levels, and a decrease in plasma aldosterone concentration. Serum potassium levels are not significantly affected by Irbesartan alone at the recommended doses. Irbesartan does not inhibit ACE (kininase-II), an enzyme which generates angiotensin-II and also degrades bradykinin into inactive metabolites. Irbesartan does not require metabolic activation for its activity.

Pharmacokinetic properties
Absorption
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.
Distribution
Plasma protein binding is approximately 96%, with negligible binding to cellular blood components. The volume of distribution is 53 - 93 liters. Following oral or intravenous administration of ^{14}C-Irbesartan, 80-85% of the circulating plasma radioactivity is attributable to unchanged Irbesartan.
Biotransformation
Irbesartan is metabolized by the liver via glucuronide conjugation and oxidation. The major circulating metabolite is Irbesartan glucuronide (approximately 6%). In vitro studies indicate that Irbesartan is primarily oxidized by the cytochrome P450 enzyme CYP2C9; isoenzyme CYP3A4 has negligible effect.
Elimination
Irbesartan and its metabolites are eliminated by both biliary and renal pathways. After either oral or IV administration of ^{14}C-Irbesartan, about 20% of the radioactivity is recovered in the urine, and the remainder in the feces. Less than 2% of the dose is excreted in the urine as unchanged Irbesartan.
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.

INDICATIONS
Ibecard®- IPS is indicated in adults for the treatment of essential hypertension.
It is also indicated for the treatment of renal disease in adult patients with hypertension and type 2 diabetes mellitus as part of an antihypertensive medicinal product regimen.

CONTRAINDICATIONS
- Hypersensitivity to the active substance, or to any of the excipients.
- Second and third trimesters of pregnancy.

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, diarrhea 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 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 across all subgroups, in an analysis carried out in the study with patients with advanced renal disease. In particular, they appeared less favorable in women and non-white subjects.
- Hyperkalemia: As with other medicinal products that affect the renin-angiotensin-aldosterone system, hyperkalemia 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, azotemia, oliguria, or rarely acute renal failure. As with any antihypertensive agent, excessive blood pressure decrease in patients with ischemic cardiopathy or ischemic 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.
- 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.
- Pediatric population: Irbesartan has been studied in pediatric populations aged 6 to 16 years old but the current data are insufficient to support an extension of the use in children until further data become available.

Ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed. 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.

PREGNANCY AND LACTATION
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, hyperkalemia).
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.
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.
Irbesartan had no effect upon fertility of treated rats and their offspring up to the dose levels including the first signs of parental toxicity.

DRUG INTERACTIONS
- 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.
- 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

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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: In clinical studies, the pharmacokinetic of Irbesartan is not affected by hydrochlorothiazide. Irbesartan is mainly metabolized by CYP2C9 and to a lesser extent by glucuronidation. No significant pharmacokinetic or pharmacodynamic interactions were observed when Irbesartan was co-administered with warfarin, a medicinal product metabolized 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 co-administration of Irbesartan.

ADVERSE EFFECTS

In placebo-controlled trials in patients with hypertension, the overall incidence of adverse events did not differ between the Irbesartan (56.2%) and the placebo groups (56.5%). Discontinuation due to any clinical or laboratory adverse event was less frequent for Irbesartan-treated patients (3.3%) than for placebo-treated patients (4.5%). The incidence of adverse events was not related to dose (in the recommended dose range), gender, age, race, or duration of treatment.

In diabetic hypertensive patients with microalbuminuria and normal renal function, orthostatic dizziness and orthostatic hypotension were reported in 0.5% of the patients (i.e., uncommon) but in excess of placebo.

Terms marked with a star (*) refer to the adverse reactions that were additionally reported in > 2% of diabetic hypertensive patients with chronic renal insufficiency and overt proteinuria and in excess of placebo.

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.

Adverse reactions additionally reported from post-marketing experience are also listed. These adverse reactions are derived from spontaneous reports.

- Immune system disorders: Hypersensitivity reactions such as angioedema, rash, urticaria (not known).
- Metabolism and nutrition disorders: Hyperkalemia (not known).
- Nervous system disorders: Dizziness, orthostatic dizziness* (common); vertigo, headache (not known).
- Ear and labyrinth disorder: Tinnitus (not known).
- Cardiac disorders: Tachycardia (uncommon).
- Vascular disorders: Orthostatic hypotension* (common); flushing (uncommon).
- Respiratory, thoracic and mediastinal disorders: Cough (uncommon).
- Gastrointestinal disorders: Nausea/vomiting (common); diarrhea, dyspepsia/heart-burn (uncommon); dysgeusia (not known).
- Hepatobiliary disorders: Jaundice (uncommon); hepatitis, abnormal liver function (not known).
- Skin and subcutaneous tissue disorders: Leukocytoclastic vasculitis (not known).
- Musculoskeletal and connective tissue disorders: Musculoskeletal pain* (common); arthralgia, myalgia (in some cases associated with increased plasma creatine kinase levels), muscle cramps (not known).
- Renal and urinary disorders: Impaired renal function including cases of renal failure in patients at risk (not known).
- Reproductive system and breast disorders: Sexual dysfunction (uncommon).
- General disorders and administration site conditions: Fatigue (common); chest pain (uncommon).
- Investigations: Hyperkalemia* occurred more often in diabetic patients treated with Irbesartan than with placebo. In diabetic hypertensive patients with microalbuminuria and normal renal function, hyperkalemia (≥ 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, hyperkalemia (≥ 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 (very 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 hemoglobin*, which was not clinically significant, has been observed (common).

- Pediatric population: In a randomized trial of 318 hypertensive children and adolescents aged 6 to 16 years, the following adverse reactions occurred in the 3-week double-blind phase: Headache (7.9%), hypotension (2.2%), dizziness (1.9%), cough (0.9%). In the 26-week open-label period of this trial the most frequent laboratory abnormalities observed were creatinine increases (6.5%) and elevated CK values in 2% of child recipients.

DOSAGE AND ADMINISTRATION

The usual recommended initial and maintenance dose is 150 mg once daily, with or without food. Ibecard®- IPS 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 hemodialyzed patients and in the elderly over 75 years.

In patients insufficiently controlled with 150 mg once daily, the dose of Ibecard® - IPS 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 Ibecard® - IPS.

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 Ibecard® - IPS 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 hemodialysis.

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.

Pediatric population

The safety and efficacy of Ibecard® - IPS in children aged 0 to 18 has not been established but no recommendation on a posology can be made.

Method of Administration

For oral use.

OVERDOSAGE

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. 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 hemodialysis.

STORAGE CONDITIONS

Store below 30°C.

Keep in original pack in intact conditions.

Date of revision: September 2019.

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

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