Ibecard® Plus

Irbesartan / Hydrochlorothiazide

FORMS AND PRESENTATION

Ibecard® Plus 150/12.5: Film coated tablets: Box of 30.
Ibecard® Plus 300/12.5: Film coated tablets: Box of 30.
Ibecard® Plus 300/25: Film coated tablets: Box of 30.

COMPOSITION

Ibecard® Plus 150/12.5: Each film coated tablet contains Irbesartan 150mg and Hydrochlorothiazide 12.5mg.
Ibecard® Plus 300/12.5: Each film coated tablet contains Irbesartan 300mg and Hydrochlorothiazide 12.5mg.
Ibecard® Plus 300/25: Each film coated tablet contains Irbesartan 300mg and Hydrochlorothiazide 25mg.
Excipients: Lactose, Microcrystalline Cellulose, Povidone, Sodium Starch Glycolate, Magnesium Stearate, Hypromellose, Titanium Dioxide, Polyethylene Glycol, Red Iron Oxide, Yellow Iron Oxide, Black Iron Oxide (Ibecard® Plus 300/25).

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Therapeutic class: Agents acting on the renin-angiotensin system.
ATC code: C09DA04.
Ibecard® Plus is a combination of an angiotensin-II receptor antagonist, Irbesartan, and a thiazide diuretic, Hydrochlorothiazide. The combination of these ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.
Irbesartan is a potent, orally active, selective angiotensin-II receptor (AT1 subtype) antagonist. It is expected to block all actions of angiotensin-II mediated by the AT1 receptor, regardless of the source or route of synthesis of angiotensin-II. The selective antagonism of the angiotensin-II (AT1) receptors results in increases in plasma renin levels and angiotensin-II levels, and a decrease in plasma aldosterone concentration. Serum potassium levels are not s significantly affected by Irbesartan alone at the recommended doses in patients without risk of electrolyte imbalance. 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.
Hydrochlorothiazide is a thiazide diuretic. The mechanism of antihypertensive effect of thiazide diuretics is not fully known. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. The diuretic action of Hydrochlorothiazide reduces plasma volume, increases plasma renin activity, increases aldosterone secretion, with consequent increases in urinary potassium and bicarbonate loss, and decreases in serum potassium. Presumably through blockade of the renin-angiotensin-aldosterone system, co-administration of Irbesartan tends to reverse the potassium loss associated with these diuretics. With Hydrochlorothiazide, onset of diuresis occurs in 2 hours, and peak effect occurs at about 4 hours, while the action persists for approximately 6-12 hours.

Pharmacokinetic properties

Concomitant administration of Hydrochlorothiazide and Irbesartan has no effect on the pharmacokinetics of either medicinal product.
Irbesartan and Hydrochlorothiazide are orally active agents and do not require biotransformation for their activity. Following oral administration of Ibecard® Plus, the absolute oral bioavailability is 60-80% and 50-80% for Irbesartan and Hydrochlorothiazide, respectively. Food does not affect the bioavailability of Ibecard® Plus. Peak plasma concentration occurs at 1.5-2 hours after oral administration for Irbesartan and 1-2.5 hours for Hydrochlorothiazide.
Plasma protein binding of Irbesartan is approximately 96%, with negligible binding to cellular blood components. The volume of distribution for Irbesartan is 53-93 liters. Hydrochlorothiazide is 68% protein-bound in the plasma, and its apparent volume of distribution is 0.83-1.14 l/kg.
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 was observed; the mechanism for this is unknown. The total body and renal clearance are 157-176 and 3.0-3.5 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. In a study, somewhat higher plasma concentrations of Irbesartan were observed in female hypertensive patients. However, there was no difference in the half-life and accumulation of Irbesartan. No dosage adjustment is necessary in female patients. Irbesartan AUC and Cmax values were also somewhat greater in elderly subjects (≥ 65 years) than those of young subjects (18-40 years). However the terminal half-life was not significantly altered. No dosage adjustment is necessary in elderly patients. The mean plasma half-life of Hydrochlorothiazide reportedly ranges from 5-15 hours.
Following oral or intravenous administration of 14C Irbesartan, 80 85% of the circulating plasma radioactivity is attributable to unchanged Irbesartan. 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. Irbesartan and its metabolites are eliminated by both biliary and renal pathways. After either oral or intravenous administration of 14C 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. Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidneys. At least 61% of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier, and is excreted in breast milk.

INDICATIONS

Ibecard® Plus is indicated in the treatment of essential hypertension.
This fixed dose combination is indicated in adult patients whose blood pressure is not adequately controlled on Irbesartan or Hydrochlorothiazide alone.

CONTRAINDICATIONS

- Hypersensitivity to the active substances or to any of the excipients, or to other sulfonamide-derived substances (Hydrochlorothiazide is a sulfonamide-derived substance).
- Second and third trimesters of pregnancy.
- Severe renal impairment (creatinine clearance < 30 ml/min).
- Refractory hypokalemia, hypercalcemia.
- Severe hepatic impairment, biliary cirrhosis and cholestasis.

PRECAUTIONS

Non-melanoma skin cancer:
An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies.
Photosensitizing actions of HCTZ could act as a possible mechanism for non-melanoma skin cancer.
Patients taking HCTZ should be informed of the risk of non-melanoma skin cancer and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of HCTZ may also need to be reconsidered in patients who have experienced previous non-melanoma skin cancer.
- Hypotension - Volume-depleted patients: Ibecard® Plus has been rarely associated with symptomatic hypotension in hypertensive patients without other risk factors for hypotension. Symptomatic hypotension may be expected to 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 initiating therapy with Ibecard® Plus.
- Renal artery stenosis - 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 angiotensin converting enzyme inhibitors or angiotensin-II receptor antagonists. While this is not documented with Ibecard® Plus, a similar effect should be anticipated.
- Renal impairment and kidney transplantation: When Ibecard® Plus is used in patients with impaired renal function, a periodic monitoring of potassium, creatinine and uric acid serum levels is recommended. There is no experience regarding the administration of Ibecard® Plus in patients with a recent kidney transplantation. Ibecard® Plus should not be used in patients with severe renal impairment (creatinine clearance < 30 ml/min). Thiazide diuretic-associated azotemia may occur in patients with impaired renal function. No dosage adjustment is necessary in patients with renal impairment whose creatinine clearance is ≥ 30 ml/min. However, in patients with mild to moderate renal impairment (creatinine clearance ≥ 30 ml/min but < 60 ml/min) this fixed dose combination should be administered with caution.
- Hepatic impairment: Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. There is no clinical experience with Ibecard® Plus in patients with hepatic impairment.
- 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 Ibecard® Plus is not recommended.
- Metabolic and endocrine effects: Thiazide therapy may impair glucose tolerance. In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Latent diabetes mellitus may become manifest during thiazide therapy.
Increases in cholesterol and triglyceride levels have been associated with thiazide diuretic therapy; however at the 12.5 mg dose contained in Ibecard® Plus, minimal or no effects were reported.
Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.
- Electrolyte imbalance: As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals.
Thiazides, including Hydrochlorothiazide, can cause fluid or electrolyte imbalance (hypokalemia, hyponatremia, and hypochloremic alkalosis). Warning signs of fluid or electrolyte imbalance are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea or vomiting.
Although hypokalemia may develop with the use of thiazide diuretics, concurrent therapy with Irbesartan may reduce diuretic-induced hypokalemia. The risk of hypokalemia is greatest in patients with cirrhosis of the liver, in patients experiencing brisk diuresis, in patients who are receiving inadequate oral intake of electrolytes and in patients receiving concomitant therapy with corticosteroids or ACTH. Conversely, due to the Irbesartan component of Ibecard® Plus hyperkalemia might occur, especially in the presence of renal impairment and/or heart failure, and diabetes mellitus. Adequate monitoring of serum potassium in patients at risk is recommended. Potassium-sparing diuretics, potassium supplements or potassium-containing salts substitutes should be co-administered cautiously with Ibecard® Plus.
There is no evidence that Irbesartan would reduce or prevent diuretic-induced hyponatremia. Chloride deficit is generally mild and usually does not require treatment.
Thiazides may decrease urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.
Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesemia.
- Lithium: The combination of lithium and Ibecard® Plus is not recommended.
- Anti-doping test: Hydrochlorothiazide contained in this medicinal product could produce a positive analytic result in an anti-doping test.
- 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.
Hypersensitivity reactions to Hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.
Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazide diuretics.
Cases of photosensitivity reactions have been reported with thiazides diuretics. If photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If a re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.
- 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.
- Acute Myopia and Secondary Acute Angle-Closure Glaucoma: Sulfonamide drugs or sulfonamide derivative drugs can cause an idiosyncratic reaction, resulting in transient myopia and acute angle-closure glaucoma. While Hydrochlorothiazide is a sulfonamide, only isolated cases of acute angle-closure glaucoma have been reported so far with Hydrochlorothiazide. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug intake as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

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, Ibecard® Plus is unlikely to affect this ability. When driving vehicles or operating machines, it should be taken into account that occasionally dizziness or weariness may occur during treatment of hypertension.

PREGNANCY AND LACTATION

Angiotensin II Receptor Antagonists (AIIRAs)
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 AIIRA should be stopped immediately, and, if appropriate, alternative therapy should be started.
Exposure to AIIRAs 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 Ibecard® Plus during breast-feeding, Ibecard® Plus 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.
Hydrochlorothiazide
There is limited experience with Hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient. Hydrochlorothiazide crosses the placenta.
Based on the pharmacological mechanism of action of Hydrochlorothiazide its use during the

second and third trimester may compromise feto-placental perfusion and may cause fetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia
Hydrochlorothiazide should not be used for gestational edema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.
Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.
Since Ibecard® Plus contains Hydrochlorothiazide, it is not recommended during the first trimester of pregnancy. A switch to a suitable alternative treatment should be carried out in advance of a planned pregnancy.
Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production. The use of Ibecard® Plus during breast feeding is not recommended. If Ibecard® Plus is used during breast feeding, doses should be kept as low as possible.

DRUG INTERACTIONS

- Other antihypertensive agents: The antihypertensive effect of Ibecard® Plus may be increased with the concomitant use of other antihypertensive agents. Irbesartan and Hydrochlorothiazide (at doses up to 300 mg Irbesartan/25 mg Hydrochlorothiazide) have been safely administered with other antihypertensive agents including calcium channel blockers and beta-adrenergic blockers. Prior treatment with high dose diuretics may result in volume depletion and a risk of hypotension when initiating therapy with Irbesartan with or without thiazide diuretics unless the volume depletion is corrected first.
- 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. Furthermore, renal clearance of lithium is reduced by thiazides so the risk of lithium toxicity could be increased with Ibecard® Plus. Therefore, the combination of lithium and Ibecard® Plus is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended.
- Medicinal products affecting potassium: The potassium-depleting effect of Hydrochlorothiazide is attenuated by the potassium-sparing effect of Irbesartan. However, this effect of Hydrochlorothiazide on serum potassium would be expected to be potentiated by other medicinal products associated with potassium loss and hypokalemia (e.g. other kaliuretic diuretics, laxatives, amphotericin, carbenoxolone, penicillin G sodium). Conversely, based on the experience with the use of other medicinal products that blunt 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 sodium) may lead to increases in serum potassium. Adequate monitoring of serum potassium in patients at risk is recommended.
- Medicinal products affected by serum potassium disturbances: Periodic monitoring of serum potassium is recommended when Ibecard® Plus is administered with medicinal products affected by serum potassium disturbances (e.g. digitalis glycosides, antiarrhythmics).
- 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 coadministered 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.
- Additional information on Hydrochlorothiazide interactions: when administered concurrently, the following medicinal products may interact with thiazide diuretics:

Alcohol: Potentiation of orthostatic hypotension may occur.
Antidiabetic medicinal products (oral agents and insulins): Dosage adjustment of the antidiabetic medicinal product may be required.
Colestyramine and Colestipol resins: Absorption of Hydrochlorothiazide is impaired in the presence of anionic exchange resins. Ibecard® Plus should be taken at least one hour before or four hours after these medications.
Corticosteroids, ACTH: Electrolyte depletion, particularly hypokalemia, may be increased.
Digitalis glycosides: Thiazide induced hypokalemia or hypomagnesemia favor the onset of digitalis-induced cardiac arrhythmias.
Non-steroidal anti-inflammatory drugs: The administration of a non-steroidal anti-inflammatory drug may reduce the diuretic, natriuretic and antihypertensive effects of thiazide diuretics in some patients.
Pressor amines (e.g. noradrenaline): The effect of pressor amines may be decreased, but not sufficiently to preclude their use.
Nondepolarizing skeletal muscle relaxants (e.g. tubocurarine): The effect of nondepolarizing skeletal muscle relaxants may be potentiated by Hydrochlorothiazide.
Antigout medicinal products: Dosage adjustments of antigout medicinal products may be necessary as Hydrochlorothiazide may raise the level of serum uric acid. Increase in dosage of probenecid or sulfinpyrazone may be necessary. Co-administration of thiazide diuretics may increase the incidence of hypersensitivity reactions to allopurinol.
Calcium salts: Thiazide diuretics may increase serum calcium levels due to decreased excretion. If calcium supplements or calcium sparing medicinal products (e.g. vitamin D therapy) must be prescribed, serum calcium levels should be monitored and calcium dosage adjusted accordingly.
Carbamazepine: Concomitant use of carbamazepine and Hydrochlorothiazide has been associated with the risk of symptomatic hyponatremia. Electrolytes should be monitored during concomitant use. If possible, another class of diuretics should be used.
Other interactions: the hyperglycemic effect of beta-blockers and diazoxide may be enhanced by thiazides. Anticholinergic agents (e.g. atropine, beperiden) may increase the bioavailability of thiazide-type diuretics by decreasing gastrointestinal motility and stomach emptying rate. Thiazides may increase the risk of adverse effects caused by amantadine. Thiazides may reduce the renal excretion of cytotoxic medicinal products (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.

ADVERSE EFFECTS

Irbesartan/Hydrochlorothiazide combination

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.
- Investigations: Increases in blood urea nitrogen (BUN), creatinine and creatine kinase (common); decreases in serum potassium and sodium (ucommon).
- Cardiac disorders: Syncope, hypotension, tachycardia, edema (uncommon).
- Nervous system disorders: dizziness (common); orthostatic dizziness (ucommon); headache (not known).
- Ear and labyrinth disorders: Tinnitus (not known).
- Respiratory, thoracic and mediastinal disorders: Cough (not known).
- Gastrointestinal disorders: Nausea/vomiting (common); diarrhea (uncommon); dyspepsia, dysgeusia (not known).
- Renal and urinary disorders: Abnormal urination (common); impaired renal function including isolated cases of renal failure in patients at risk (not known).
- Musculoskeletal and connective tissue disorders: Swelling extremity (uncommon); arthralgia, Myalgia (not known).
- Metabolism and nutrition disorders: Hyperkalemia (not known).
- Vascular disorders: Flushing (uncommon).
- General disorders and administration site conditions: Fatigue (common).
- Immune system disorders: cases of hypersensitivity reactions such as angioedema, rash, urticaria (not known).
- Hepatobiliary disorders: Jaundice (uncommon); hepatitis, abnormal liver function (not known).
- Reproductive system and breast disorders: Sexual dysfunction, libido changes (uncommon).

Additional information on individual components
In addition to the adverse reactions listed above for the combination product, other adverse reactions previously reported with one of the individual components may be potential adverse reactions with Ibecard® Plus.

Irbesartan

- General disorders and administration site conditions: Chest pain (uncommon).

Hydrochlorothiazide

- Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma) - (Frequency 'not known')
- Investigations: electrolyte imbalance, hyperuricemia, glycosuria, hyperglycemia, increases in cholesterol and triglycerides (not known).
- Cardiac disorders: cardiac arrhythmias (not known).
- Blood and lymphatic system disorders: aplastic anemia, bone marrow depression, neutropenia/agranulocytosis, hemolytic anemia, leucopenia, thrombocytopenia (not known).
- Nervous system disorders: vertigo, paraesthesia, light-headedness, restlessness (not known).
- Eye disorders: transient blurred vision, xanthopsia (not known).
- Respiratory, thoracic and mediastinal disorders: respiratory distress (including pneumonitis and pulmonary edema) (not known).
- Gastrointestinal disorders: pancreatitis, anorexia, diarrhea, constipation, gastric irritation, sialadenitis, loss of appetite (not known).
- Renal and urinary disorders: interstitial nephritis, renal dysfunction (not known).
- Skin and subcutaneous tissue disorders: anaphylactic reactions, toxic epidermal necrolysis, necrotizing angitis (vasculitis, cutaneous vasculitis), cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, photosensitivity reactions, rash, urticaria (not known).
- Musculoskeletal and connective tissue disorders: weakness, muscle spasm (not known).
- Vascular disorders: postural hypotension (not known).
- General disorders and administration site conditions: fever (not known).
- Hepatobiliary disorders: jaundice (intrahepatic cholestatic jaundice) (not known).
- Psychiatric disorders: depression, sleep disturbances (not known).

The dose dependent adverse events of Hydrochlorothiazide (particularly electrolyte disturbances) may increase when titrating the Hydrochlorothiazide.

DOSAGE AND ADMINISTRATION

Posology
Ibecard® Plus can be taken once daily, with or without food.
Dose titration with the individual components (i.e. Irbesartan and Hydrochlorothiazide) may be recommended.
When clinically appropriate direct change from monotherapy to the fixed combinations may be considered:
- Ibecard® Plus 150/12.5 may be administered in patients whose blood pressure is not adequately controlled with Hydrochlorothiazide or Irbesartan 150 mg alone.
- Ibecard® Plus 300/12.5 may be administered in patients insufficiently controlled by Irbesartan 300 mg or by Ibecard® Plus 150/12.5.
- Ibecard® Plus 300/25 may be administered in patients insufficiently controlled by Ibecard® Plus 300/12.5.

Doses higher than 300 mg Irbesartan/25 mg Hydrochlorothiazide once daily are not recommended.
When necessary, Ibecard® Plus may be administered with another antihypertensive medicinal product.
Renal impairment: Due to the Hydrochlorothiazide component, Ibecard® Plus is not recommended for patients with severe renal dysfunction (creatinine clearance < 30 ml/min). Loop diuretics are preferred to thiazides in this population. No dosage adjustment is necessary in patients with renal impairment whose renal creatinine clearance is ≥ 30 ml/min.
Hepatic impairment: Ibecard® Plus is not indicated in patients with severe hepatic impairment. Thiazides should be used with caution in patients with impaired hepatic function. No dosage adjustment of Ibecard® Plus is necessary in patients with mild to moderate hepatic impairment.
Elderly patients: No dosage adjustment of Ibecard® Plus is necessary in elderly patients.
Pediatric population: Ibecard® Plus is not recommended for use in children and adolescents because the safety and efficacy have not been established. No data are available.
Method of Administration
For oral use.

OVERDOSAGE

No specific information is available on the treatment of overdose with Ibecard® Plus. The patient should be closely monitored, and the treatment should be symptomatic and supportive. Management depends on the time since ingestion and the severity of the symptoms. Suggested measures include induction of emesis and/or gastric lavage. Activated charcoal may be useful in the treatment of overdose. Serum electrolytes and creatinine should be monitored frequently. If hypotension occurs, the patient should be placed in a supine position, with salt and volume replacements given quickly.
The most likely manifestations of Irbesartan overdose are expected to be hypotension and tachycardia; bradycardia might also occur.
Overdose with Hydrochlorothiazide is associated with electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. The most common signs and symptoms of overdose are nausea and somnolence. Hypokalemia may result in muscle spasms and/or accentuate cardiac arrhythmias associated with the concomitant use of digitalis glycosides or certain anti-arrhythmic medicinal products.
Irbesartan is not removed by hemodialysis. The degree to which Hydrochlorothiazide is removed by hemodialysis has not been established.

STORAGE CONDITIONS

Store below 30°C.
Keep in original pack in intact conditions.

Date of revision: September 2019.

Exclusively distributed by IPS.

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
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Benta S.A.L.
Dbayeh - Lebanon