ARBI-D® Tablet

آربی-ڈی ٹیبلیٹ

(Irbesartan/Hydrochlorothiazide USP)

COMPOSITION

ARBI D 150 mg/12.5mg Tablet
Each film coated tablet contains:
Irbesartan 150mg and Hydrochlorothiazide 12.5mg

ARBI D 300 mg/12.5mg Tablet
Each film coated tablet contains:
Irbesartan 300mg and Hydrochlorothiazide 12.5mg

ARBI D 300 mg/25mg Tablet
Each film coated tablet contains:
Irbesartan 300mg and Hydrochlorothiazide 25mg
[USP specs]

WARNING: FETAL TOXICITY
The use of Angiotensin II Receptor Antagonists (AIIRAs) is not recommended during the first trimester of pregnancy. The use of Angiotensin II Receptor Antagonists (AIIRAs) is contraindicated during the second and third trimesters of pregnancy.

DESCRIPTION

ARBI-D tablets are a combination of an angiotensin II receptor antagonist (AT1 subtype), irbesartan and a thiazide diuretic, hydrochlorothiazide (HCT). Irbesartan is a non-peptide compound, chemically described as a 2-butyl-3-[p-(o-1H-tetrazol-5ylphenyl)benzyl]-1,3-diazaspiro[4.4]non-1-en-4-one.
Its empirical formula is $C_{25}H_{28}N_6O$. Hydrochlorothiazide is 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1dioxide. Its empirical formula is $C_7H_8ClN_3O_4S_2$

CLINICAL PHARMACOLOGY

Mechanism of Action

Irbesartan
Irbesartan is a potent, orally active, selective angiotensin-II receptor (type AT1) 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 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.

Hydrochlorothiazide
Hydrochlorothiazide is a thiazide diuretic. The mechanism of antihypertensive effect of thiazide diuretic 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.

PHARMACOKINETICS

Absorption

Irbesartan and Hydrocholorothiazide
Irbesartan and hydrochlorothiazide are orally active agents and do not require biotransformation for their activity. Following oral administration of irbesartan/hydrochlorothiazide, the absolute oral bioavailability is 60-80 % and 50-80 % for irbesartan and hydrochlorothiazide, respectively. Food does not affect the bioavailability of irbesartan/hydrochlorothiazide. Peak plasma concentration occurs at 1.5-2 hours after oral administration for irbesartan and 1-2.5 hours for hydrochlorothiazide.

Distribution

Irbesartan
Irbesartan is 90% bound to serum proteins (primarily albumin and α1-acid glycoprotein) with negligible binding to cellular components of blood. The average volume of distribution is 53 to 93 liters. Studies in animals indicate that radiolabeled Irbesartan weakly crosses the blood-brain barrier and placenta.

Hydrochlorothiazide
Hydrochlorothiazide is 68 % protein-bound in the plasma, and its apparent volume of distribution is 0.83-1.14 l/kg.

Metabolism

Irbesartan
Irbesartan is an orally active agent that does not require biotransformation into an active form. Irbesartan is metabolized via glucuronide conjugation and oxidation. Following oral or intravenous administration of 14C- labeled irbesartan, more than 80% of the circulating plasma radioactivity is attributable to unchanged irbesartan. In vitro studies indicate irbesartan is oxidized primarily by CYP2C9; metabolism by CYP3A4 is negligible.

Hydrochlorothiazide
Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidneys.

Elimination

Irbesartan
Total plasma and renal clearances of Irbesartan are in the range of 157 to 176 mL/min and 3.0 to 3.5 mL/min, respectively. The terminal elimination half-life of Irbesartan averages 11 to 15 hours. Steady-state concentrations are achieved within 3 days. Irbesartan and its metabolites are eliminated by both biliary and renal pathways. After either oral or IV 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.

Hydrochlorothiazide
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. In patients with creatinine clearance < 20 ml/min, the elimination half-life of hydrochlorothiazide was reported to increase to 21 hours.

INDICATIONS

• 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.
• Arbi-D may also be used as initial therapy in patients who are likely to need multiple drugs to achieve their blood pressure goals

DOSAGE AND ADMINISTRATION

• Arbi-D (Irbesartan/Hydrochlorothiazide) 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.

• Arbi-D (Irbesartan/Hydrochlorothiazide) 150 mg/12.5 mg may be administered in patients whose blood pressure is not adequately controlled with hydrochlorothiazide or irbesartan 150 mg alone;
• Arbi-D (Irbesartan/Hydrochlorothiazide) 300 mg/12.5 mg may be administered in patients insufficiently controlled by irbesartan 300 mg or by Irbesartan Hydrochlorothiazide Arbi-D 150 mg/12.5 mg.
• Arbi-D (Irbesartan/Hydrochlorothiazide) 300 mg/25mg may be administered in patients insufficiently controlled by Irbesartan Hydrochlorothiazide Arbi-D 300 mg/12.5 mg.

Doses higher than 300 mg Irbesartan/25mg hydrochlorothiazide once daily are not recommended. Dose increments should be made after 1-2 weeks of therapy.

• When necessary, Arbi-D (Irbesartan/Hydrochlorothiazide) may be administered with another Anti-hypertensive product.

Dosing consideration in special populations

Renal impairment:
Due to the hydrochlorothiazide component, Arbi-D (Irbesartan/Hydrochlorothiazide) 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:
Arbi-D (Irbesartan/Hydrochlorothiazide) Tablet 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 Irbesartan/Hydrochlorothiazide is necessary in patients with mild to moderate hepatic impairment.

Elderly patients:
No dosage adjustment of Arbi-D (Irbesartan/Hydrochlorothiazide) film-coated Tablets is necessary in elderly patients.

Paediatric population:
Arbi-D (Irbesartan/Hydrochlorothiazide) Tablets are not recommended for use in children and adolescents due to a lack of data on safety and efficacy.

Method of administration
For oral use.

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 hypokalaemia, hypercalcaemia.
• Severe hepatic impairment, biliary cirrhosis and cholestasis.
• The concomitant use of Irbesartan/Hydrochlorothiazide with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (creatinine clearance <60ml/min/1.73 m²).
• Due to its HCT component Irbesartan/HCT tablets are contraindicated in anuric patients

WARNINGS AND PRECAUTIONS

Hypotension- Volume-depleted patients
Arbi-D (Irbesartan/Hydrochlorothiazide) 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 Irbesartan/Hydrochlorothiazide.

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 Irbesartan/Hydrochlorothiazide,a similar effect should be anticipated.

Renal impairment and kidney transplantation
When Irbesartan /Hydrochlorothiazide 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 Irbesartan /Hydrochlorothiazide Arbi-D patients with recent kidney transplantation. Irbesartan /Hydrochlorothiazide 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 ≥30ml/min but <60 ml/min) this fixed dose combination should be administered with caution and monitoring of renal function

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.

The concomitant use of Irbesartan/Hydrochlorothiazide with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (creatinine clearance <60ml/min.

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. Irbesartan/HCT must not be used in patients with severe hepatic impairment. No dosage adjustment of Arbi-D is required in patients with mild to moderate 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 Irbesartan/Hydrochlorothiazide 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 12.5mg dose contained in Irbesartan/HCT, minimal or no effects were reported.

Hyperuricaemia 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, hyponatraemia, 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 Irbesartan/ Hydrochlorothiazide 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 Irbesartan/Hydrochlorothiazide. There is no evidence that Irbesartan would reduce or prevent diuretic-induced hyponatraemia. 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 hypercalcaemia 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 hypomagnesaemia.

Lithium
The combination of lithium and Irbesartan/HCT 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 anti-hypertensive 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 AIIRAs therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive 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. Also see CONTRAINDICATIONS

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.

Effects on 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/HCT 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.

ADVERSE REACTIONS

Investigations:	Common:	increases in blood urea nitrogen (BUN), creatinine and creatine kinase
	Uncommon:	decreases in serum potassium and sodium
Cardiac disorders:	Uncommon:	syncope, hypotension, tachycardia, oedema
Nervous system disorders:	Common:	dizziness
	Uncommon:	orthostatic dizziness
	Not known:	headache
Ear and labyrinth disorders:	Not known:	tinnitus
Respiratory, thoracic and mediastinal disorders:	Not known:	cough
Gastrointestinal disorders:	Common:	nausea/vomiting
	Uncommon:	diarrhoea
	Not known:	dyspepsia, dysgeusia
Renal and urinary disorders:	Common:	abnormal urination
	Not known:	impaired renal function including isolated cases of renal failure in patients at risk (see section 4.4)

Musculoskeletal and connective tissue disorders:	Uncommon:	swelling extremity
	Not known:	arthralgia, myalgia
Metabolism and nutrition disorders:	Not known:	hyperkalaemia
Vascular disorders:	Uncommon:	flushing
General disorders and administration site conditions:	Common:	fatigue
Immune system disorders:	Not known:	cases of hypersensitivity reactions such as angioedema, rash, urticaria
Hepatobiliary disorders:	Uncommon:	jaundice
	Not known:	hepatitis, abnormal liver function
Reproductive system and breast disorders:	Uncommon:	sexual dysfunction, libido changes

DRUG INTERACTIONS

Other antihypertensive agents
The antihypertensive effect of Irbesartan/Hydrochlorothiazide may be increased with the concomitant use of other antihypertensive agents. Irbesartan and hydrochlorothiazide (at doses up to 300 mg Irbesartan/25mg 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 Irbesartan Hydrochlorothiazide. Therefore, the combination of lithium and Irbesartan Hydrochlorothiazide is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Drugs 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 hypokalaemia (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.

Drugs affected by serum potassium disturbances
Periodic monitoring of serum potassium is recommended when Irbesartan/Hydrochlorothiazide 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 (> 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.

Administration of a non-steroidal anti-inflammatory agent, including a selective COX-2 inhibitor can also reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing, and thiazide diuretics. Response to therapy should be closely monitored.

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.
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. See [CONTRAINDICATIONS and WARNINGS and PRECAUTIONS]

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 when given with HCT as thiazides may alter glucose tolerance.

Colestyramine and Colestipol resins:
Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Irbesartan Hydrochlorothiazide should be taken at least one hour before or four hours after the administration of these resins.

Corticosteroids, ACTH:
Electrolyte depletion, particularly hypokalaemia, may be increased.

Digitalis glycosides:
Thiazide induced hypokalaemia or hypomagnaesemia favour the onset of digitalis-induced cardiac arrhythmias.

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 drugs:
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 hypnoatraemia. Electrolytes should be monitored during concomitant use. If possible, another class of diuretics should be used.

Other interactions:
The hyperglycaemic 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.

USE IN SPECIAL POPULATIONS

Pregnancy

Irbesartan/HCT belongs to US-FDA pregnancy category D

Irbesartan
The use of angiotensin II receptor antagonists (AIIRAs) including Irbesartan is not recommended during the first trimester of pregnancy. The use of AIIRAs is contraindicated during the second and third trimester of pregnancy.
Unless continued AIIRAs therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs including Irbesartan 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, 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.

Hydrochlorthiazide
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 HCT 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 Irbesartan Hydrochlorothiazide contains hydrochlorozide 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.

Nursing mothers

Irbesartan
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 breastfeeding are preferable, especially while nursing a newborn or preterm infant.

It is unknown whether Irbesartan or its metabolites are excreted in human milk. Available pharmacodynamics/toxicological data in rats have shown excretion of irbesartan or its metabolites in milk.

Hydrochlorthiazide
Hydrochlorthiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production. The use of hydrochlorthiazide during breast-feeding is not recommended. If hydrochlorthiazide is used during breast-feeding, doses should be kept as low as possible.

Renal impairment
No dosage adjustment is necessary in patients with renal impairment whose renal creatinine clearance is ≥ 30 ml/min (see DOSAGE AND ADMINISTRATION)

Hepatic impairment
No dosage adjustment of Irbesartan Hydrochlorothiazide is necessary in patients with mild to moderate hepatic impairment (see DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS)

OVERDOSE
No specific information is available on the treatment of overdose with irbesartan/HCT. 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 (hypokalaemia, hypochloremia, hyponatraemia) and dehydration resulting from excessive diuresis. The most common signs and symptoms of overdose are nausea and somnolence. Hypokalaemia 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 haemodialysis. The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

PRESENTATION
ARBI-D® 150/12.5 is available in pack of 10 tablets.
ARBI-D® 300/12.5 is available in pack of 10 tablets.
ARBI-D® 300/25 is available in pack of 14 tablets.

INSTRUCTIONS
As advised by the physician.
Keep all medicines out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.
Protect from heat, light and moisture.
Store below 30°C.

For more information on our products
call PharmAssist helpline 0800-82222
Monday to Friday 9:00 am to 6:00 pm
or email us at : pharmassist@pharmevo.biz

ہدایات:
ڈاکٹر کی ہدایات کے مطابق استعمال کریں۔
تمام دوائیں بچّوں کی پہنچ سے دُور رکھیں۔
صرف رجسٹرڈ ڈاکٹر کے نسخہ پر ہی فروخت کی جائے۔
روشنی، گرمی اور نمی سے محفوظ، 30°C سے کم درجہ حرارت پر رکھیں۔

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DI:ARBD 01 12/2016

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