Gizlan-Plus®

Irbesartan / Hydrochlorothiazide

DESCRIPTION:
Gizlan-Plus® is a combination of angiotensin-II receptor antagonists, irbesartan, and a thiazide diuretic, hydrochlorothiazide. The combination of these ingredients has an additive antihypertensive effect, reducing blood pressure to greater degree than either component alone.
Inactive ingredients: Lactose monohydrate, croscarmellose sodium, pregelatinized starch, magnesium stearate, colloidal anhydrous silica, microcrystalline cellulose, hypromellose, macrogol, titanium dioxide, talc, red iron oxide (E172), yellow iron oxide (E172), **Gizlan-Plus®** 300 mg/25mg contains black iron oxide (E172) as well.

PHARMACOLOGY:
Irbesartan belongs to a group of medicines known as angiotensin-II receptor antagonists. Angiotensin-II is a substance produced in the body that binds to receptors in blood vessels causing them to tighten. This results in an increase in blood pressure. Irbesartan prevents the binding of angiotensin-II to these receptors, causing the blood vessels to relax and the blood pressure to lower.
Hydrochlorothiazide is one of a group of medicines (called thiazide diuretics) that causes increased urine output and so causes a lowering of blood pressure.

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.

CONTRAINDICATIONS:
- Hypersensitivity to the active substances, or to any of the excipients, or to other sulfonamide-derived substances.
- During second and third trimesters of pregnancy.
- Severe renal impairment (creatinine clearance < 30 ml/min).
- Refractory hypokalaemia, hypercalcaemia.
- Severe hepatic impairment, biliary cirrhosis and cholestasis.

SIDE 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.
Frequency for adverse reactions detected by spontaneous reports is described as "not known".
Investigations; Common: increases in blood urea nitrogen, 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 warnings and precautions).
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: Not known: hepatitis, abnormal liver function.
Reproductive system and breast disorders: Uncommon: sexual dysfunction, libido changes.
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 **Gizlan-Plus®**.
Adverse reactions reported with the use of irbesartan alone:
General disorders and administration site conditions: Uncommon: chest pain.
Adverse reactions (regardless of relationship to medicinal product) reported with the use of hydrochlorothiazide alone for which the frequency is unknown:
Investigations: electrolyte imbalance (including hypokalaemia and hyponatraemia, see warnings and precautions), hyperuricaemia, glycosuria, hyperglycaemia, increases in cholesterol and triglycerides.
Cardiac disorders: cardiac arrhythmias.
Blood and lymphatic system disorders: aplastic anaemia, bone marrow depression, neutropenia/agranulocytosis, haemolytic anaemia, leucopenia, thrombocytopenia.
Nervous system disorders: vertigo, paraesthesia, light-headedness, restlessness.
Eye disorders: transient blurred vision, xanthopsia.
Respiratory, thoracic and mediastinal disorders: respiratory distress (including pneumonitis and pulmonary oedema).
Gastrointestinal disorders: pancreatitis, anorexia, diarrhoea, constipation, gastric irritation, sialadenitis, loss of appetite.
Renal and urinary disorders: interstitial nephritis, renal dysfunction.
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.
Musculoskeletal and connective tissue disorders: weakness, muscle spasm.
Vascular disorders: postural hypotension.
General disorders and administration site conditions: fever.
Hepatobiliary disorders: jaundice (intrahepatic cholestatic jaundice).
Psychiatric disorders: depression, sleep disturbances.
Note: The dose dependent adverse events of hydrochlorothiazide (particularly electrolyte disturbances) may increase when titrating the hydrochlorothiazide.

WARNINGS AND PRECAUTIONS:
Hypotension - Volume-depleted patients: **Gizlan-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, and diarrhoea or vomiting. Such conditions should be corrected before initiating therapy with **Gizlan-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 **Gizlan-Plus®**, a similar effect should be anticipated.
Renal impairment and kidney transplantation: When **Gizlan-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 **Gizlan-Plus®** in patients with recent kidney transplantation. **Gizlan-Plus®** should not be used in patients with severe renal impairment (creatinine clearance < 30 ml/min) (see contraindications).
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 Irbesartan / Hydrochlorothiazide 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 **Gizlan-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, 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 (hypokalaemia, 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 hypokalaemia may develop with the use of thiazide diuretics, concurrent therapy with irbesartan may reduce diuretic-induced hypokalaemia. The risk of hypokalaemia 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 **Gizlan-Plus®** hyperkalaemia 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 **Gizlan-Plus®** (see drug interactions).
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 hypomagnaesemia.
Lithium: The combination of lithium and **Gizlan-Plus®** is not recommended (see drug interactions).
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 (see side effects). 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 (see contraindications).
Lactation:
Because no information is available regarding the use of **Gizlan-Plus®** during breast-feeding, **Gizlan-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.
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, **Gizlan-Plus®** 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 of hypertension. **Gizlan-Plus®** tablets contain lactose: If the patient has been told by the doctor that he has intolerance to some sugars, the patient should contact the doctor before taking this medicinal product. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

DRUG INTERACTIONS:
Other antihypertensive agents: the antihypertensive effect of **Gizlan-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 (see warnings and precautions).
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 **Gizlan-Plus®**. Therefore, the combination of lithium and **Gizlan-Plus®** is not recommended (see warnings and precautions). 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 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, and 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 (see warnings and precautions).
Medicinal products affected by serum potassium disturbances: periodic monitoring of serum potassium is recommended when **Gizlan-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: 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.
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 (see warnings and precautions).
Colestyramine and Colestipol resins: Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. **Gizlan-Plus®** should be taken at least one hour before or four hours after these medications.
Corticosteroids, ACTH: Electrolyte depletion, particularly hypokalaemia, may be increased.
Digitalis glycosides: Thiazide induced hypokalaemia or hypomagnaesemia favour the onset of digitalis-induced cardiac arrhythmias (see warnings and precautions).
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.
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.

DOSAGE AND ADMINISTRATION:
Gizlan-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:
-**Gizlan-Plus®** 150 mg/12.5 mg may be administered in patients whose blood pressure is not adequately controlled with hydrochlorothiazide or irbesartan 150 mg alone.
-**Gizlan-Plus®** 300 mg/12.5 mg may be administered in patients insufficiently controlled by irbesartan 300 mg or by **Gizlan-Plus®** 150 mg/12.5 mg.
-**Gizlan-Plus®** 300 mg/25 mg may be administered in patients insufficiently controlled by **Gizlan-Plus®** 300 mg/12.5 mg.
Doses higher than 300 mg irbesartan/25 mg hydrochlorothiazide once daily are not recommended.
When necessary, **Gizlan-Plus®** may be administered with another antihypertensive medicinal product (see drug interactions).
The tablets should be swallowed with a sufficient amount of fluid (e.g. one glass of water). Patient can take **Gizlan-Plus®** with or without food. Patient should try to take the daily dose at about the same time each day. It is important that the patient continue to take **Gizlan-Plus®** until the doctor tells him otherwise.
The maximal blood pressure lowering effect should be reached 6-8 weeks after beginning treatment.
Renal impairment: due to the hydrochlorothiazide component, **Gizlan-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 (see contraindications and warnings and precautions).
Hepatic impairment: **Gizlan-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 **Gizlan-Plus®** is necessary in patients with mild to moderate hepatic impairment (see contraindications).
Elderly patients: no dosage adjustment of **Gizlan-Plus®** is necessary in elderly patients.
Paediatric patients: **Gizlan-Plus®** is not recommended for use in children and adolescents due to a lack of data on safety and efficacy.
Missed doses:
If the patient accidentally misses a daily dose, the patient just takes the next dose as normal. The patient should not take a double dose to make up for forgotten individual doses.

OVERDOSAGE:
No specific information is available on the treatment of overdose with **Gizlan-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 (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.

PRESENTATIONS:
Gizlan-Plus® 150/12.5 Film Coated Tablets: Packs of 30 and 500 tablets. Each tablet contains 150 mg irbesartan and 12.5 mg hydrochlorothiazide.
Gizlan-Plus® 300/12.5 Film Coated Tablets: Packs of 30 and 500 tablets. Each tablet contains 300 mg irbesartan and 12.5 mg hydrochlorothiazide.
Gizlan-Plus® 300/25 Film Coated Tablets: Packs of 30 and 500 tablets. Each tablet contains 300 mg irbesartan and 25 mg hydrochlorothiazide.

STORAGE CONDITIONS:
Store below 30°C.

This is a medicament
- *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 you the medicament.*
- *The doctor and the pharmacist are experts in medicine, its benefits and its risks.*
- *Do not, by yourself, interrupt the period of treatment prescribed.*
- *Do not repeat the same prescription without consulting your doctor.*

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