ZIOREL PLUS®

Irbesartan and Hydrochlorothiazide film-coated tablets

USE IN PREGNANCY
When pregnancy is detected, discontinue Ziorel Plus® as soon as possible. When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus.

DESCRIPTION

Ziorel Plus® is a combination of an angiotensin II receptor antagonist (AT_1 subtype), Irbesartan and a thiazide diuretic, Hydrochlorothiazide (HCTZ).
Ziorel Plus® is available for oral administration in salmon colored film-coated tablets containing either 150 mg or 300 mg of Irbesartan combined with 12.5 mg of Hydrochlorothiazide.
Inactive ingredients include: Lactose monohydrate; Microcrystalline cellulose; Pregelatinized starch; Croscarmellose sodium; Silicon dioxide and Magnesium stearate.
Film coating solution: Hydroxypropylmethylcellulose; Titanium dioxide; Lactose; Polyethylene glycol; Iron oxide and Carnauba wax.

CLINICAL PHARMACOLOGY

Irbesartan
Angiotensin II is a potent vasoconstrictor formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system (RAS) and also stimulates aldosterone synthesis and secretion by adrenal cortex, cardiac contraction, renal resorption of sodium, activity of the sympathetic nervous system and smooth muscle cell growth. Irbesartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively binding to the AT_1 angiotensin II receptor. There is also an AT_2 receptor in many tissues, but it is not involved in cardiovascular homeostasis. Irbesartan is a specific competitive antagonist of AT_1 receptors with a much greater affinity (more than 8500-fold) for the AT_1 receptor than for the AT_2 receptor and no agonist activity. Blockade of the AT_1 receptor removes the negative feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and circulating angiotensin II do not overcome the effects of Irbesartan on blood pressure. Irbesartan does not inhibit ACE or renin or affect other hormone receptors or ion channels known to be involved in the cardiovascular regulation of blood pressure and sodium homeostasis. Because Irbesartan does not inhibit ACE, it does not affect the response to bradykinin; whether this has clinical relevance is not known.

Hydrochlorothiazide
Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. Indirectly, the diuretic action of Hydrochlorothiazide reduces plasma volume, with consequent increases in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so coadministration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with these diuretics. The mechanism of the antihypertensive effect of thiazides is not fully understood.

INDICATIONS AND USAGE

Ziorel Plus® tablets is indicated for the treatment of hypertension.
Ziorel Plus® may be used in patients whose blood pressure is not adequately controlled on monotherapy.
Ziorel Plus® may also be used as initial therapy in patients who are likely to need multiple drugs to achieve their blood pressure goals.
The choice of Ziorel Plus® as initial therapy for hypertension should be based on an assessment of potential benefits and risks. Patients with stage 2 (moderate or severe) hypertension are at relatively high risk for cardiovascular events (such as strokes, heart attacks and heart failure), kidney failure and vision problems, so prompt treatment is clinically relevant. The decision to use a combination as initial therapy should be individualized and may be shaped by considerations such as the baseline blood pressure, the target goal and the incremental likelihood of achieving goal with a combination compared with monotherapy.

CONTRAINDICATIONS

- Ziorel Plus® is contraindicated in patients who are hypersensitive to any component of this product.
- Because of the Hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

WARNINGS AND PRECAUTIONS

Fetal/Neonatal Morbidity and Mortality: Ziorel Plus® can cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. In several dozen published cases, angiotensin converting enzyme (ACE) inhibitor use during the second and third trimesters of pregnancy was associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure and death. Similar renal findings occur in reproductive toxicology studies in rats. Thiazides cross the placenta and use of thiazides during pregnancy is associated with a risk of fetal or neonatal jaundice, thrombocytopenia and possibly other adverse reactions that have occurred in adults.
Hypotension in Volume- or Salt-Depleted Patients: Excessive reduction of blood pressure was rarely seen in patients with uncomplicated hypertension treated with Irbesartan alone (< 0.1%) or with Irbesartan-Hydrochlorothiazide (approximately 1%). Initiation of antihypertensive therapy may cause symptomatic hypotension in patients with intravascular volume- or sodium-depletion, e.g. in patients treated vigorously with diuretics or in patients on dialysis. Such volume depletion should be corrected prior to administration of antihypertensive therapy.
If hypotension occurs, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.
Hypersensitivity Reaction:
Hydrochlorothiazide: 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.
Systemic Lupus Erythematosus:
Hydrochlorothiazide: Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.
Lithium Interaction:
Hydrochlorothiazide: Lithium generally should not be given with thiazides.
Electrolyte and Metabolic Imbalances:
Irbesartan-Hydrochlorothiazide: In double-blind clinical trials of various doses of Irbesartan and Hydrochlorothiazide, the incidence of hypertensive patients who developed hypokalemia (serum potassium < 3.5 mEq/L) was 7.5% versus 6.0% for placebo; the incidence of hyperkalemia (serum potassium > 5.7 mEq/L) was < 1.0% versus 1.7% for placebo. No patient discontinued due to increases or decreases in serum potassium. On average, the combination of Irbesartan and Hydrochlorothiazide had no effect on serum potassium. Higher doses of Irbesartan ameliorated the hypokalemic response to Hydrochlorothiazide.
Hydrochlorothiazide: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia and gastrointestinal disturbances such as nausea and vomiting.
Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present or after prolonged therapy.
Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g. increased ventricular irritability).
Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.
Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.
Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.
In diabetic patients, dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus, latent diabetes mellitus may become manifest during thiazide therapy.
The antihypertensive effects of the drug may be enhanced in the post-sympathectomy patient.
If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy.
Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.
Thiazides may decrease urinary calcium excretion. Thiazides may cause 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.
Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.
Hepatic Impairment:
Hydrochlorothiazide: 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.
Impaired Renal Function:
As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure), treatment with ACE inhibitors has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Irbesartan would be expected to behave similarly. In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or BUN have been reported. There has been no known use of Irbesartan in patients with unilateral or bilateral renal artery stenosis, but a similar effect should be anticipated.
Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

USE IN SPECIFIC POPULATIONS

Pregnancy
Pregnancy Category D
See Warnings and Precautions

Ziorel Plus® contains both Irbesartan (an angiotensin II receptor antagonist) and Hydrochlorothiazide (a thiazide diuretic). When administered during the second or third trimester of pregnancy, drugs that act directly on the renin-angiotensin system (RAS) can cause fetal and neonatal morbidity and death. Thiazides cross the placenta and use of thiazides during pregnancy is associated with a risk of fetal or neonatal jaundice, thrombocytopenia and possibly other adverse reactions that have occurred in adults. Ziorel Plus® can cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.
Angiotensin II receptor antagonists, like Irbesartan and ACE inhibitors exert similar effects on the RAS. In several dozen published cases, ACE inhibitor use during the second and third trimesters of pregnancy was associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure and death. Oligohydramnios was also reported, presumably from decreased fetal renal function. In this setting, oligohydramnios was associated with fetal limb contractures, craniofacial deformation and hypoplastic lung development. Prematurity, intrauterine growth retardation and patent ductus arteriosus were also reported, although it is not clear whether these occurrences were due to exposure to the drug. These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester.
When pregnancy occurs in a patient using Ziorel Plus®, the physician should discontinue Ziorel Plus® treatment as soon as possible. The physician should inform the patient about potential risks to the fetus based on the time of gestational exposure to Ziorel Plus® (first trimester only or later). If exposure occurs beyond the first trimester, an ultrasound examination should be done.
In rare cases when another antihypertensive agent cannot be used to treat the pregnant patient, serial ultrasound examinations should be performed to assess the intraamniotic environment. Routine fetal testing with non-stress tests, biophysical profiles and/or contraction stress tests may be appropriate based on gestational age and standards of care in the community. If oligohydramnios occurs in these situations, individualized decisions about continuing or discontinuing Ziorel Plus® treatment and about pregnancy management should be made by the patient, her physician and experts in the management of high risk pregnancy. Patients and physicians should be aware that oligohydramnios may not appear until after the fetus has sustained irreversible injury.
Infants with histories of in utero exposure to Ziorel Plus® should be closely observed for hypotension, oliguria and hyperkalemia. If oliguria occurs, these infants may require blood pressure and renal perfusion support. Exchange transfusion or dialysis may be required to reverse hypotension and/or support decreased renal function.
Radioactivity was present in the rat and rabbit fetus during late gestation and in rat milk following oral doses of radiolabeled Irbesartan.

Nursing Mothers
It is not known whether Irbesartan is excreted in human milk, but Irbesartan or some metabolite of Irbesartan is secreted at low concentration in the milk of lactating rats.
Thiazides appear in human milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.
Pediatric Use
Safety and effectiveness in pediatric patients have not been established.
Geriatric Use
No overall differences in safety or effectiveness were observed between patients more than 65 years and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS
Clinical Trials Experience
Irbesartan-Hydrochlorothiazide
Irbesartan-Hydrochlorothiazide has been evaluated for safety in 1694 patients treated for essential hypertension in 6 clinical trials. No adverse events peculiar to this combination drug product have been observed. Adverse events have been limited to those that were reported previously with Irbesartan or Hydrochlorothiazide.
The overall incidence of adverse events was similar with the combination and placebo. In general, treatment with Irbesartan-Hydrochlorothiazide was well tolerated. For the most part, adverse events have been mild and transient in nature and have not required discontinuation of therapy. In controlled clinical trials, discontinuation of Irbesartan-Hydrochlorothiazide therapy due to clinical adverse events was required in only 3.6%. This incidence was significantly less ($p=0.023$) than the 6.8% of patients treated with placebo who discontinued therapy.
In the double-blind controlled clinical trials, the following adverse events reported with Irbesartan-Hydrochlorothiazide occured in ≥ 1% of patients, and more often on the Irbesartan-Hydrochlorothiazide combination than on placebo, regardless of drug relationship: chest pain, fatigue, influenza, tachycardia, abdominal pain, dyspepsia/heartburn, nausea/vomiting, allergy, musculoskeletal pain, dizziness, orthostatic dizziness and abnormal urination.
The following adverse events were also reported at a rate of 1% or greater, but were as, or more, common in the placebo group: headache, sinus abnormality, cough, URI, pharyngitis, diarrhea, rhinitis, urinary tract infection, rash, anxiety/nervousness and muscle cramp.
Adverse events occured at about the same rates in men and women, older and younger patients.

Irbesartan
Other adverse events that have been reported with Irbesartan, without regard to causality, are listed below:
Body as a Whole: fever, chills, facial edema, upper extremity edema
Cardiovascular: flushing, hypertension, cardiac murmur, myocardial infarction, angina pectoris, arrhythmic/conduction disorder, cardio-respiratory arrest, heart failure, hypertensive crisis.
Dermatologic: pruritus, dermatitis, ecchymosis, facial erythema, urticaria
Endocrine/Metabolic/Electrolyte Imbalances: sexual dysfunction, libido change, gout
Gastrointestinal: constipation, oral lesion, gastroenteritis, flatulence, abdominal distention
Musculoskeletal/Connective Tissue: extremity swelling, muscle cramp, arthritis, muscle ache, musculoskeletal chest pain, joint stiffness, bursitis, muscle weakness
Nervous System: sleep disturbance, numbness, somnolence, emotional disturbance, depression, paresthesia, tremor, transient ischemic attack, cerebrovascular accident
Renal/Genitourinary: abnormal urination, prostate disorder
Respiratory: epistaxis, tracheobronchitis, congestion, pulmonary congestion, dyspnea, wheezing
Special Senses: vision disturbance, hearing abnormality, ear infection, ear pain, conjunctivitis.

Hydrochlorothiazide
Other adverse events that have been reported with Hydrochlorothiazide, without regard to causality, are listed below:
Body as a Whole: weakness
Digestive: pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation
Hematologic: aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia
Hypersensitivity: purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions
Metabolic: hyperglycemia, glycosuria, hyperuricemia
Musculoskeletal: muscle spasm
Nervous System/Psychiatric: restlessness
Renal: renal failure, renal dysfunction, interstitial nephritis
Skin: erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis
Special Senses: transient blurred vision, xanthopsia

Post-Marketing Experience
The following adverse reactions have been identified during post-approval use of Irbesartan-Hydrochlorothiazide. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: seriousness of the reaction, frequency of reporting or strength of causal connection to Irbesartan-Hydrochlorothiazide.
The following have been very rarely reported: urticaria; angioedema (involving swelling of the face, lips, pharynx and/or tongue) and hepatitis. Hyperkalemia has been rarely reported.
Very rare cases of jaundice have been reported with Irbesartan.
Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

Laboratory Abnormalities
In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of Irbesartan-Hydrochlorothiazide.
Creatinine, Blood Urea Nitrogen: Minor increases in blood urea nitrogen (BUN) or serum creatinine were observed in 2.3% and 1.1%, respectively, of patients with essential hypertension treated with Irbesartan-Hydrochlorothiazide alone. No patient discontinued taking Irbesartan-Hydrochlorothiazide due to increased BUN. One patient discontinued taking Irbesartan-Hydrochlorothiazide due to a minor increase in serum creatinine.
Liver Function Tests: Occasional elevations of liver enzymes and/or serum bilirubin have occurred. In patients with essential hypertension treated with Irbesartan-Hydrochlorothiazide alone, one patient was discontinued due to elevated liver enzymes.
Serum Electrolytes: [See Warnings and Precautions].

DRUG INTERACTIONS
Irbesartan
No significant drug-drug interactions have been reported with Irbesartan.

Hydrochlorothiazide
When administered concurrently the following drugs may interact with thiazide diuretics:
- Alcohol, Barbiturates or Narcotics: potentiation of orthostatic hypotension may occur.
- Antidiabetic Drugs (oral agents and insulin): dosage adjustment of the antidiabetic drug may be required.
- Other Antihypertensive Drugs: additive effect or potentiation.
- Cholestyramine and Colestipol Resins: absorption of Hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the Hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85% and 43%, respectively.
- Corticosteroids, ACTH: intensified electrolyte depletion, particularly hypokalemia.
- Pressor Amines (e.g. Norepinephrine): possible decreased response to pressor amines but not sufficient to preclude their use.
- Skeletal Muscle Relaxants, Nondepolarizing (e.g. Tubocurarine): possible increased responsiveness to the muscle relaxant.
- Lithium: should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity.
- Non-steroidal Anti-inflammatory Drugs: in some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when Irbesartan-Hydrochlorothiazide tablets and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

PATIENT COUNSELING INFORMATION
Pregnancy
Female patients of childbearing age should be told that use of drugs like Ziorel Plus® during the second or third trimesters of pregnancy can cause serious problems in the fetus and infant including: low blood pressure, poor development of skull bones, kidney failure and death. These effects have not occurred with drug exposure limited to the first trimester. Women using Ziorel Plus® who become pregnant should notify their physician as soon as possible.

Symptomatic Hypotension
Patients using Ziorel Plus® should be told that they may feel lightheaded, especially during the first days of use. Patients should inform their physician if they feel lightheaded or faint. If fainting occurs, the patient should stop using Ziorel Plus® and contact the prescribing doctor.
Patients using Ziorel Plus® should be told that getting dehydrated can lower their blood pressure too much and lead to lightheadedness and possible fainting. Dehydration may occur with excessive sweating, diarrhea, or vomiting and with not drinking enough liquids.

OVERDOSAGE
Irbesartan
No data are available in regard to overdosage in humans. However, daily doses of 900 mg for 8 weeks were well tolerated. The most likely manifestations of overdosage are expected to be hypotension and tachycardia; bradycardia might also occur from overdose. Irbesartan is not removed by hemodialysis.
Laboratory determinations of serum levels of Irbesartan are not widely available and such determinations have, in any event, no established role in the management of Irbesartan overdose.

Hydrochlorothiazide
The most common signs and symptoms of overdose observed in humans are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias. The degree to which Hydrochlorothiazide is removed by hemodialysis has not been established. The oral LD_{50} of Hydrochlorothiazide is greater than 10 g/kg in both mice and rats.

DOSAGE AND ADMINISTRATION
General Considerations
The side effects of Irbesartan are generally rare and apparently independent of dose; those of Hydrochlorothiazide are a mixture of dose-dependent (primarily hypokalemia) and dose-independent phenomena (e.g. pancreatitis), the former much more common than the latter.
Maximum antihypertensive effects are attained within 2 to 4 weeks after a change in dose.
Ziorel Plus® may be administered with or without food.
Ziorel Plus® may be administered with other antihypertensive agents.
Renal impairment: The usual regimens of therapy with Ziorel Plus® may be followed as long as the patient's creatinine clearance is > 30 mL/min. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so Ziorel Plus® is not recommended.
Hepatic impairment: No dosage adjustment is necessary in patients with hepatic impairment.
Add-On Therapy
In patients not controlled on monotherapy with Irbesartan or Hydrochlorothiazide, the recommended doses of Ziorel Plus®, in order of increasing mean effect, are Irbesartan-Hydrochlorothiazide 150/12.5 mg, 300/12.5 mg and 300/25 mg. The largest incremental effect will likely be in the transition from monotherapy to 150/12.5 mg.
Replacement Therapy
Ziorel Plus® may be substituted for the titrated components.
Initial Therapy
The usual starting dose is Ziorel Plus® 150/12.5 mg once daily. The dosage can be increased after 1 to 2 weeks of therapy to a maximum of two tablets 150/12.5 mg administered once daily as needed to control blood pressure. Ziorel Plus® is not recommended as initial therapy in patients with intravascular volume depletion [see Warnings and Precautions].

STORAGE CONDITIONS: Store in a dry place below 30°C, protected from light. Do not refrigerate.

PRESENTATION
Ziorel Plus® 150/12.5 mg and 300/12.5 mg are available in blister packs of 30 tablets.
Not all strengths may be marketed.

KEEP MEDICAMENT OUT OF REACH OF CHILDREN.

Do not exceed the prescribed dose.

Do not use after expiry date.

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 you 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.
- Do not repeat the same prescription without consulting your doctor.

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P15776-01
Rev. No. 09/2014