# ZIOREL

Irbesartan film-coated tablets

**USE IN PREGNANCY**
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. When pregnancy is detected, Ziorel® should be discontinued as soon as possible.

## DESCRIPTION

Ziorel® (Irbesartan) is an angiotensin II receptor ($AT_1$ subtype) antagonist.
Ziorel® is available for oral administration in white film coated tablets containing 150 mg or 300 mg of Irbesartan. Inactive ingredients include: Lactose Monohydrate; Microcrystalline cellulose; Pregelatinized starch; Croscarmellose sodium; Silicon dioxide and Magnesium stearate. The film coating consists of: Carnauba wax; Polyvinyl alcohol; Titanium dioxide; Talc; Polyethylene glycol and Lecithin.

## CLINICAL PHARMACOLOGY

*Mechanism of Action*
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.

## INDICATIONS AND USAGE

*Hypertension*
Ziorel® is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.
*Nephropathy in Type 2 Diabetic Patients*
Ziorel® is indicated for the treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria (>300 mg/day) in patients with type 2 diabetes and hypertension. In this population, Irbesartan reduces the rate of progression of nephropathy as measured by the occurrence of doubling of serum creatinine or end-stage renal disease (need for dialysis or renal transplantation).

## CONTRAINDICATIONS

Ziorel® is contraindicated in patients who are hypersensitive to any component of this product.

## WARNINGS

*Fetal/Neonatal Morbidity and Mortality*
Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin-converting-enzyme inhibitors. When pregnancy is detected, Ziorel® should be discontinued as soon as possible.
The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation and hypoplastic lung development. Prematurity, intrauterine growth retardation and patent ductus arteriosus have also been 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.
Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of Ziorel® as soon as possible.
Rarely (probably less often than once in every thousand pregnancies), no alternative to a drug acting on the renin-angiotensin system will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.
If oligohydramnios is observed, Ziorel® should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST) or biophysical profiling (BPP) may be appropriate depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.
Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

*Hypotension in Volume- or Salt-depleted Patients*
Excessive reduction of blood pressure was rarely seen (<0.1%) in patients with uncomplicated hypertension. 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 Ziorel® or a low starting dose should be used. 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.

## PRECAUTIONS

*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 angiotensin-converting-enzyme inhibitors has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Ziorel® 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.

**Information for Patients**
*Pregnancy*
Female patients of childbearing age should be told about the consequences of second and third trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

*Drug Interactions*
No significant drug-drug pharmacokinetic (or pharmacodynamic) interactions have been found in interaction studies with hydrochlorothiazide, digoxin, warfarin and nifedipine.
In separate studies of patients receiving maintenance doses of warfarin, hydrochlorothiazide or digoxin, Irbesartan administration for 7 days had no effect on the pharmacodynamics of warfarin (prothrombin time) or pharmacokinetics of digoxin. The pharmacokinetics of Irbesartan were not affected by coadministration of nifedipine or hydrochlorothiazide.

*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. 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*
Irbesartan, in a study at a dose of up to 4.5 mg/kg/day, once daily, did not appear to lower blood pressure effectively in pediatric patients age 6 to 16 years. Irbesartan has not been studied in pediatric patients less than 6 years old.

*Geriatric Use*
No overall differences in effectiveness or safety were observed between geriatric subjects and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

## ADVERSE REACTIONS

*Hypertension*
Treatment with Irbesartan was well-tolerated, with an incidence of adverse events similar to placebo. These events generally were mild and transient with no relationship to the dose of Irbesartan.
In placebo-controlled clinical trials, discontinuation of therapy due to a clinical adverse event was required in 3.3% of patients treated with Irbesartan, versus 4.5% of patients given placebo. In placebo-controlled clinical trials, the following adverse event experiences reported in at least 1% of patients treated with Irbesartan and at a higher incidence versus placebo excluding those too general to be informative and those not reasonably associated with the use of drug because they were associated with the condition being treated or are very common in the treated population, include: diarrhea (3% vs 2%), dyspepsia/heartburn (2% vs 1%) and fatigue (4% vs 3%).

The following adverse events occurred at an incidence of 1% or greater in patients treated with Irbesartan, but were at least as frequent or more frequent in patients receiving placebo: abdominal pain, anxiety/nervousness, chest pain, dizziness, edema, headache, influenza, musculoskeletal pain, pharyngitis, nausea/vomiting, rash, rhinitis, sinus abnormality, tachycardia and urinary tract infection.
Irbesartan use was not associated with an increased incidence of dry cough, as is typically associated with ACE inhibitor use.
The incidence of hypotension or orthostatic hypotension was low in Irbesartan-treated patients (0.4%), unrelated to dosage and similar to the incidence among placebo-treated patients (0.2%). Dizziness, syncope and vertigo were reported with equal or less frequency in patients receiving Irbesartan compared with placebo.
In addition, the following potentially important events occurred in less than 1% of the patients and at least 5 patients (0.3%) receiving Irbesartan in clinical studies, and those less frequent, clinically significant events (listed by body system). It cannot be determined whether these events were causally related to Irbesartan:
*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, other eye disturbance, eyelid abnormality, ear abnormality

*Nephropathy in Type 2 Diabetic Patients*
In clinical studies in patients with hypertension and type 2 diabetic renal disease, the adverse drug experiences were similar to those seen in patients with hypertension with the exception of an increased incidence of orthostatic symptoms (dizziness, orthostatic dizziness and orthostatic hypotension) observed in IDNT (Irbesartan in Diabetic Nephropathy Trial) (proteinuria ≥900 mg/day, and serum creatinine ranging from 1.0-3.0 mg/dL). In this trial, orthostatic symptoms occurred more frequently in the Irbesartan group (dizziness 10.2%, orthostatic dizziness 5.4%, orthostatic hypotension 5.4%) than in the placebo group (dizziness 6.0%, orthostatic dizziness 2.7%, orthostatic hypotension 3.2%).

*Post-Marketing Experience*
The following have been very rarely reported in post-marketing experience: urticaria; angioedema (involving swelling of the face, lips, pharynx and/or tongue); increased liver function tests; jaundice and hepatitis. Hyperkalemia has been rarely reported.
Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

*Laboratory Test Findings*
In controlled clinical trials, clinically important differences in laboratory tests were rarely associated with administration of Irbesartan.

## OVERDOSAGE

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.

## DOSAGE AND ADMINISTRATION

Ziorel® may be administered with other antihypertensive agents and with or without food.

*Hypertension*
The recommended initial dose of Ziorel® is 150 mg once daily. Patients requiring further reduction in blood pressure should be titrated to 300 mg once daily.
A low dose of a diuretic may be added, if blood pressure is not controlled by Ziorel® alone. Hydrochlorothiazide has been shown to have an additive effect. Patients not adequately treated by the maximum dose of 300 mg once daily are unlikely to derive additional benefit from a higher dose or twice-daily dosing.
No dosage adjustment is necessary in elderly patients, or in patients with hepatic impairment or mild to severe renal impairment.

*Nephropathy in Type 2 Diabetic Patients*
The recommended target maintenance dose is 300 mg once daily. There are no data on the clinical effects of lower doses of Irbesartan on diabetic nephropathy

*Volume- and Salt-depleted Patients*
A lower initial dose of Irbesartan (75 mg) is recommended in patients with depletion of intravascular volume or salt (e.g. patients treated vigorously with diuretics or on hemodialysis)

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

## PRESENTATION

Ziorel® 150 and 300 mg are available in blister packs of 30 tablets.

**KEEP MEDICAMENT OUT OF REACH AND SIGHT 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.

Manufactured by
**ALGORITHM S.A.L.** Zouk Mosbeh, Lebanon


P15774-01
Rev. No. 02/2014