DIRECTIONS FOR USE

1. Hypertension

1.1 Hypertension

Irbesartan tablets are indicated for the treatment of hypertension, to lower blood pressure. In general, achieve blood pressure goals as quickly as possible. Consider titration to another antihypertensive to reach blood pressure goal. It is not known whether any other antihypertensive is more effective than irbesartan in this regard. See Clinical Studies (14.2).

Hypertension should be part of an integrated management approach which includes diet control, weight loss, exercise, limitation of alcohol ingestion, and moderation of other risk factors, such as hyperlipidemia and smoking. If these measures are not satisfactory, pharmacological therapy should be initiated.

Control of high blood pressure reduces the risk of stroke, heart attack, and other cardiovascular complications. See Clinical Trials Experience (14.1) and Information for Patients (17).

2. Diabetic Nephropathy

2.1 Diabetic Nephropathy

Irbesartan has been evaluated in patients with diabetic nephropathy and is indicated for the treatment of diabetic nephropathy in addition to blood pressure control. In addition to blood pressure control, treatment of diabetic nephropathy is best accomplished by cooperation between patients and their physicians. See Use in Specific Populations (8.4).

2.2 Nephropathy in Type 2 Diabetic Patients

Nephropathy in type 2 diabetic patients: The most common adverse reactions were hypotenion, diarrhea, and nasopharyngitis.

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3. Pregnancy

3.1 Pregnancy

Ibuprofen tablets USP 300 mg are available for oral administration as unscored tablets containing 300 mg each of ibuprofen. Ibuprofen tablets USP contain the following inactive ingredients: colloidial silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose and pregelatinized starch.

4. Clinical Pharmacology

4.1 Clinical Pharmacology

6.1 Laboratory Studies

6.2 Laboratory Studies

6.3 Laboratory Studies

7.1 Laboratory Studies

7.2 Laboratory Studies

7.3 Laboratory Studies

8.2 Pregnancy

8.3 Pregnancy

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13.2 Pregnancy
12.2 Pharmacodynamics

In healthy subjects, single oral irbesartan doses of up to 300 mg produced dose-dependent increases in plasma levels with peak concentrations occurring within 2-6 hours. The area under the curve (AUC) increased approximately proportionally to the dose, whereas the terminal elimination half-life was dose independent. Irbesartan is not metabolized in man; it is excreted in the urine as the active parent compound and its metabolites. Total plasma clearance is approximately 170 mL/min and is independent of dose and sex. In women, the clearance is about 30% greater than in men. The metabolism of irbesartan is similar in Asian and Caucasian populations. In vitro data reveal no significant differences in enzymatic activity between these two populations.

12.3 Pharmacokinetics

Absorption

Irbesartan is rapidly absorbed after oral administration of 150 mg and 300 mg doses. The mean time to peak concentration was 1.5 to 2.5 hours. Irbesartan achieved high (>90%) plasma exposure at doses of 150 mg and 300 mg. The absolute bioavailability of irbesartan is about 40%.

Distribution

Irbesartan is approximately 98% 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 radioactive irbesartan weakly crosses the blood-brain barrier and placenta. Irbesartan is excreted in the milk of lactating women.

Elimination

Total plasma and renal clearances are in the range of 157 to 176 mL/min and 3.0 to 3.5 mL/min, respectively. The terminal half-life of irbesartan was 11 to 16 hours. Steady-state concentrations are achieved within 3 days. Limited accumulation of irbesartan (~20%) is observed in plasma upon repeated once-daily dosing and is not clinically relevant.

Metabolism

Irbesartan is an orally active agent that does not require bioactivation into an active form. Irbesartan is metabolized via glucuronidation and conjugation. Following oral or intravenous administration of 14C-labeled irbesartan, more than 80% of the circulating plasma radioactivity is attributable to unchanged irbesartan. The primary circulating metabolite is the inactive irbesartan glucuronide conjugate (approximately 6%). The remaining oxidative metabolites do not add appreciably to irbesartan’s pharmacologic activity. In vitro studies indicate that irbesartan is oxidized primarily by CYP2C8, metabolism by CYP3A4 is negligible.

Excretion

Irbesartan and its metabolites are excreted both by biliary and renal routes. Following either oral or intravenous administration of 14C-labeled irbesartan, about 20% of radioactivity is recovered in the urine and the remainder in the feces, as irbesartan or irbesartan glucuronide.

Specific Populations

Sex

No sex-related differences in pharmacokinetics are observed in healthy elderly (65-80 years) or in healthy young (18-40 years) subjects. In studies of hypertensive patients, there is no sex difference in half-life or accumulation, but the mean Cmax is higher in women compared with men (approximately 11%-44%). No sex-related dosage adjustment is necessary.

Race/Ethnicity

In healthy black subjects, irbesartan AUC values are approximately 25% greater than whites; there is no difference in Cmax values.

Renal Impairment

The pharmacokinetics of irbesartan are not altered in patients with renal impairment or in patients on hemodialysis. Irbesartan is not removed by hemodialysis. No dosage adjustment is necessary in patients with mild to severe renal impairment unless a patient with renal impairment is also volume depleted (see Warnings and Precautions (5.2) and Dosage and Administration (2.4)).

Hepatic Insufficiency

The pharmacokinetics of irbesartan following repeated oral administration are not significantly affected in patients with mild to moderate cirrhosis of the liver. No dosage adjustment is necessary in patients with hepatic insufficiency.

Drug-Drug Interactions

In vitro studies show significant inhibition of the formation of oxidized irbesartan metabolites with the known cytochrome P450 CYP 2C9 substrates/inhibitors sulfaphenazole, tolbutamide and indinavir. However, in clinical studies the consequences of concomitant irbesartan on the pharmacodynamics of warfarin were negligible. Based on in vitro data, no interaction would be expected with drugs whose metabolism is dependent upon cytochrome P450 2C19 (e.g., verapamil, diltiazem, phenprocoumon, bupropion, theophylline, imatinib). In separate studies of patients receiving maintenance doses of warfarin, hydrochlorothiazide, or digoxin, irbesartan administration for 7 days has no effect on the pharmacodynamics of warfarin (prothrombin time) or pharmacokinetics of digoxin. The pharmacokinetics of irbesartan are not affected by coadministration of indinavir or hydrochlorothiazide.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of carcinogenicity was observed when irbesartan was administered at doses up to 500 mg/kg/day (males/females, respectively) in rats and 1000 mg/kg/day in mice for up to 2 years. In female and male rats, 500 mg/kg/day provided an average systemic exposure to irbesartan [AUC(0-24h), bound plus unbound] about 3 and 11 times, respectively, the average systemic exposure in humans receiving the maximum recommended dose (MRD) of 300 mg irbesartan/day, whereas 1000 mg/kg/day (administered to females only) provided an average systemic exposure about 21 times that reported for humans at the MRD. For male and female mice, 1000 mg/kg/day provided an exposure to irbesartan about 3 and 5 times, respectively, that reported for humans at the MRD. Irbesartan was not mutagenic in a battery of in vitro tests ( Ames microbial test, rat hepatocyte URA repair test, V79 mammalian-cell forward gene mutation assay). Irbesartan was retested in an in vitro test for induction of chromosomal aberrations (in vitro-human lymphocyte assay, in vivo-mouse micronucleus test). Irbesartan had no adverse effects on fertility or mating of male or female rats at oral doses 650 mg/kg/day, the highest dose providing a systemic exposure to irbesartan (AUC(0-24h), bound plus unbound) about 5 times that found in humans receiving the MRD of 300 mg/day.

13.2 Animal Toxicology and/or Pharmacology

When pregnant rats were treated with irbesartan from Day 0 to Day 20 of gestation (oral doses of 50 mg/kg/day, 150 mg/kg/day, and 500 mg/kg/day), increased incidences of renal pelvic cavitation, hydronephrosis and/or absence of renal papilla were observed in fetuses at doses 150 mg/kg/day (approximately equivalent to the maximum recommended human dose [MRHD], 300 mg/day, on a body surface area basis). Subcutaneous injection was found in fetuses at doses ≥300 mg/kg/day (approximately 4 times the MRHD on a body surface area basis). At these doses, no fetal anomalies were observed in rats in which irbesartan exposure (oral doses of 50, 150, and 500 mg/kg/day) was limited to gestation days 6 to 15. They appear to reflect late gestational effects of the drug. In pregnant rabbits, oral doses of 30 mg of irbesartan/kg/day were associated with maternal mortality and abortion. Surviving females receiving this dose (about 1.5 times the MRHD on a body surface area basis) had a slight increase in early deliveries and a corresponding decrease in live litters. Irbesartan was found to cross the placental barrier in rats and rabbits. In a study of the rat, the effect was somewhat less in blacks (usually a low-renin population).

14 CLINICAL STUDIES

14.1 Hypertension

The antihypertensive effects of irbesartan were examined in 7 placebo-controlled 8- to 12-week trials in patients with torrential diastolic blood pressures of 90 to 110 mmHg. Doses of 1 to 900 mg were included in these trials in order to fully explore the dose-range of irbesartan. These studies allowed comparison of once- or twice-daily regimens at 150 mg/day, comparison of peak and trough effects, and comparisons of response by sex, age, and race. Two of the seven placebo-controlled trials identified above examined the antihypertensive effects of irbesartan and hydrochlorothiazide in combination. The 7 studies of 16 weeks’ duration included a total of 1915 patients randomized to irbesartan (1-900 mg) and 611 patients randomized to placebo. One-dose daily of 150 mg and 300 mg produced statistically and clinically significant decreases in systolic and diastolic blood pressure with trough (24 hour minus post-dose) effects after 6 to 12 weeks of treatment compared to placebo, of about -9.105-6 mmHg and -10.3-8 mmHg, respectively. No further increase in effect was seen at dosages greater than 300 mg. The dose-response relationships for effects on systolic and diastolic pressure are shown in Figures 1 and 2.

In controlled trials, the addition of irbesartan to hydrochlorothiazide doses of 6.25 mg, 12.5 mg, or 25 mg produced further dose-related reductions in blood pressure similar to those observed with the same monotherapy dose of irbesartan HCl fixed dose. Irbesartan HCl also had an additive effect.

One-dose daily-administration of therapeutic doses of irbesartan gave peak effects at around 3 to 6 hours and, in one ambulatory blood pressure monitoring study, again around 11 hours. Peak effects were seen with both once- and twice-daily dosing. Two-point-to-peak ratios for systolic and diastolic response were generally between 80% to 70%. In a continuous ambulatory blood pressure monitoring study, once-daily dosing produced a 150 mg and a 24 mg daily dose. In hypertensive patients, there was essentially no change in average heart rate at 2 weeks of therapy. The effect was somewhat less in blacks (usually a low-renin population).

In healthy subjects, single oral irbesartan doses of up to 300 mg produced dose-dependent increases in plasma levels with peak concentrations occurring within 2-6 hours. The area under the curve (AUC) increased approximately proportionally to the dose, whereas the terminal elimination half-life was dose independent. Irbesartan is not metabolized in man; it is excreted in the urine as the active parent compound and its metabolites. Total plasma clearance is approximately 170 mL/min and is independent of dose and sex. In women, the clearance is about 30% greater than in men.