IRBIS 75/150/300
Irbesartan film coated tablets
75mg/150mg/300mg

IRBIS 75/150/300
Irbesartan film coated tablets 75mg/150mg/300mg

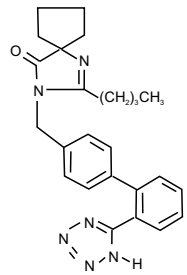
Irbesartan tablets 75 mg
Each film coated tablet contains 75 mg of Irbesartan Ph.Eur

Irbesartan tablets 150 mg
Each film coated tablet contains 150 mg of Irbesartan Ph.Eur

Irbesartan tablets 300 mg
Each film coated tablet contains 300 mg of Irbesartan Ph.Eur

DESCRIPTION

Irbesartan is an II (AT_1 subtype). Irbesartan is a non-peptide compound. Chemically described as a 2-butyl-3-[p-(o-1H-tetrazole-5-ylphenyl) benzyl]-1, 3-diazaspiro[4.4] non-1-en-4-one.
Its formula is $C_{25}H_{28}N_6O$, and the structural formula:



Irbesartan is a white to off-white crystalline powder with a molecular weight of 428.5. It is a nonpolar compound with a partition coefficient (octanol/water) of 10.1 at pH of 7.4. Irbesartan is slightly soluble in alcohol and methylene and practically insoluble in water.
Irbesartan is available for oral administration tablets containing 75 mg, 150 mg & 300 mg of Irbesartan. Inactive ingredients include: Cellulose Microcrystalline, Carmellose calcium, Povidone k-30, Silica Colloidal Anhydrous, Calcium Stearate and Opadry white.

CLINICAL PARTICULARS

Therapeutic indications

Treatment of essential hypertension.
Treatment of renal disease in patients with hypertension and type 2 diabetes mellitus as part of an antihypertensive drug regimen *(see Pharmacodynamic properties)*.

Posology and method of administration

The usual recommended initial and maintenance dose is 150 mg once daily, with or without food. Irbesartan at a dose of 150 mg once daily generally provides a better 24 hour blood pressure control than 75 mg. However, initiation of therapy with 75 mg could be considered, particularly in haemodialysed patients and in the elderly over 75 years.
In patients insufficiently controlled with 150 mg once daily, the dose of Irbesartan can be increased to 300 mg, or other anti-hypertensive agents can be added. In particular, the addition of a diuretic such as hydrochlorothiazide has been shown to have an additive effect with Irbesartan *(see Interaction with other medicinal products and other forms of interaction)*.
In hypertensive type 2 diabetic patients, therapy should be initiated at 150 mg irbesartan once daily and titrated up to 300 mg once daily as the preferred maintenance dose for treatment of renal disease. The demonstration of renal benefit of Irbesartan in hypertensive type 2 diabetic patients is based on studies where irbesartan was used in addition to other antihypertensive agents, as needed, to reach target blood pressure *(see Pharmacodynamic properties)*.

Renal impairment: no dosage adjustment is necessary in patients with impaired renal function. A lower starting dose (75 mg) should be considered for patients undergoing haemodialysis.

Intravascular volume depletion: volume and/or sodium depletion should be corrected prior to administration of Irbesartan.

Hepatic impairment: no dosage adjustment is necessary in patients with mild to moderate hepatic impairment. There is no clinical experience in patients with severe hepatic impairment.

Elderly patients: although consideration should be given to initiating therapy with 75 mg in patients over 75 years of age, dosage adjustment is not usually necessary for the elderly.

Children: safety and efficacy of Irbesartan have not been established in children.

Contraindications

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, Irbesartan should be discontinued as soon as possible.

Hypersensitivity to the active substance or to any of the excipients *(see List of excipients)*.
Second and third trimester of pregnancy *(see Special warnings and special precautions for use and Pregnancy and lactation)*. Do not administer Irbesartan with angiotensin-converting enzyme inhibitors (ACEIs) in patients with diabetic nephropathy *(see Special warnings and special precautions for use and Interaction with other medicinal products and other forms of interaction)*.
The concomitant use of Irbesartan with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (glomerular filtration rate (GFR) < 60 ml/min/1.73 m2) (see *Interaction with other medicinal products and other forms of interaction* and *Pharmacodynamic properties*).

Special warnings and special precautions for use

Intravascular volume depletion: symptomatic hypotension, especially after the first dose, may occur in patients who are volume and/or sodium depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Such conditions should be corrected before the administration of Irbesartan.

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 medicinal products that affect the renin-angiotensin-aldosterone system. While this is not documented with Irbesartan, a similar effect should be anticipated with angiotensin II receptor antagonists.

Hypoglycemia: Irbesartan may induce hypoglycemia, particularly in patients treated for diabetes. Therefore, dose adjustment of antidiabetic treatment such as repaglinide or insulin may be required (see *Undesirable effects*).

Renal impairment and kidney transplantation: when Irbesartan is used in patients with impaired renal function, a periodic monitoring of potassium and creatinine serum levels is recommended. There is no experience regarding the administration of Irbesartan in patients with a recent kidney transplantation.

Hypertensive patients with type 2 diabetes and renal disease: the effects of irbesartan both on renal and cardiovascular events were not uniform across all subgroups, in an analysis carried out in the study with patients with advanced renal disease. In particular, they appeared less favourable in women and non-white subjects *(see Pharmacodynamic properties)*.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS): The use of Irbesartan in combination with an ACEI is contraindicated in patients with diabetic nephropathy (see Interaction with other medicinal products and other forms of interaction).
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 (see *Interaction with other medicinal products and other forms of interaction Interaction and Pharmacodynamic properties*). 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.

Hyperkalaemia: as with other medicinal products that affect the renin-angiotensin-aldosterone system, hyperkalaemia may occur during the treatment with Irbesartan, especially in the presence of renal impairment, overt proteinuria due to diabetic renal disease, and/or heart failure. Close monitoring of serum potassium in patients at risk is recommended *(see Interaction with other medicinal products and other forms of interaction)*.

Lithium: the combination of lithium and Irbesartan is not recommended *(see Interaction with other medicinal products and other forms of interaction)*.

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 is not recommended.

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, azotaemia, oliguria, or rarely acute renal failure *(see Interaction with other medicinal products and other forms of interaction)*. As with any antihypertensive agent, excessive blood pressure decrease in patients with ischaemic cardiopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke.
As observed for angiotensin converting enzyme inhibitors, irbesartan and the other angiotensin antagonists are apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population *(see Pharmacodynamic properties)*.

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 and Special warnings and special precautions for use)*.

Lactose: Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Interaction with other medicinal products and other forms of interaction

Diuretics and other antihypertensive agents: other antihypertensive agents may increase the hypotensive effects of irbesartan; however Irbesartan has been safely administered with other antihypertensive agents, such as beta-blockers, long-acting calcium channel blockers, and thiazide diuretics. Prior treatment with high dose diuretics may result in volume depletion and a risk of hypotension when initiating therapy with Irbesartan *(see Special warnings and special precautions for use)*.

Angiotensin-converting enzyme inhibitors (ACEIs): the use of Irbesartan in combination with an ACEI is contraindicated in patients with diabetic nephropathy and is not recommended in other patients.

Aliskiren-containing products and ACE-inhibitors: clinical trial data has shown that 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 Contraindication, Special warnings and precautions for use and Pharmacodynamic properties*).

Potassium supplements and potassium-sparing diuretics: based on experience with the use of other medicinal products that affect 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) may lead to increases in serum potassium and is, therefore, not recommended *(see Special warnings and special precautions for use)*.

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. Therefore, this combination is not recommended *(see Special warnings and special precautions for use)*. If the combination proves necessary, careful monitoring of serum lithium levels is recommended.

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: in clinical studies, the pharmacokinetic of irbesartan is not affected by hydrochlorothiazide. Irbesartan is mainly metabolised 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 metabolised 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.

Fertility, Pregnancy and lactation

Pregnancy:
The use of AIIRAs is not recommended during the first trimester of pregnancy *(see Special warnings and special precautions for use)*. The use of AIIRAs is contraindicated during the second and third trimesters of pregnancy *(see Contraindications and Special warnings and special precautions for use)*.
Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with angiotensin II receptor antagonists (AIIRAs), similar risks may exist for this class of drugs. Unless continued therapy with AIIRA 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.
Exposure to AIIRA therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). *(see Preclinical safety data)*
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 *(see also Contraindications and Special warnings and special precautions for use)*.

Lactation:
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 breast-feeding are preferable, especially while nursing a new born or preterm infant.
It is unknown whether irbesartan or its metabolites are excreted in human milk.
Available pharmacodynamic/toxicological data in rats have shown excretion of irbesartan or its metabolites in milk (see *Preclinical safety data*).

Fertility: Irbesartan had no effect upon fertility of treated rats and their offspring up to the dose levels inducing the first signs of parental toxicity (see *Preclinical safety data*).

Effects on ability to drive and use machines

Based on its pharmacodynamic properties, irbesartan is unlikely to affect the ability to drive and use machines. When driving vehicles or operating machines, it should be taken into account that dizziness or weariness may occur during treatment.

Undesirable effects

In placebo-controlled trials in patients with hypertension, the overall incidence of adverse events did not differ between the irbesartan (56.2%) and the placebo groups (56.5%). Discontinuation due to any clinical or laboratory adverse event was less frequent for irbesartan-treated patients (3.3%) than for placebo-treated patients (4.5%). The incidence of adverse events was not related to dose (in the recommended dose range), gender, age, race, or duration of treatment.
In diabetic hypertensive patients with microalbuminuria and normal renal function, orthostatic dizziness and orthostatic hypotension were reported in 0.5% of the patients (i.e., uncommon) but in excess of placebo.
The following table presents the adverse drug reactions that were reported in placebo-controlled trials in which 1,965 hypertensive patients received irbesartan. Terms marked with a star (*) refer to the adverse reactions that were additionally reported in $> 2\%$ of diabetic hypertensive patients with chronic renal insufficiency and overt proteinuria and in excess of placebo.
The frequency of adverse reactions listed below is defined using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
Adverse reactions additionally reported from post-marketing experience are also listed. These adverse reactions are derived from spontaneous reports.

Blood and lymphatic system disorders:
Not known: thrombocytopenia

Immune system disorders:
Not known: hypersensitivity reactions such as rash, urticaria, angioedema, anaphylactic reaction, anaphylactic shock

Metabolism and nutrition disorders:
Not known: hyperkalaemia

Nervous system disorders:
Common: dizziness, orthostatic dizziness*Not known: vertigo, headache

Ear and labyrinth disorders:
Not known: tinnitus

Cardiac disorders:
Uncommon: tachycardia

Vascular disorders:
Common: orthostatic hypotension*
Uncommon: flushing

Respiratory, thoracic and mediastinal disorders:
Uncommon: cough

Gastrointestinal disorders:
Common: nausea/vomiting
Uncommon: diarrhea, dyspepsia/heartburn
Very rare: dysgeusia

Heptobiliary disorders:
Uncommon: jaundice
Not Known: abnormal liver function, hepatitis

Skin and subcutaneous tissue disorders:
Not known: leukocytoclastic vasculitis

Musculoskeletal and connective tissue disorders:
Common: musculoskeletal pain*
Not known: arthralgia, myalgia (in some cases associated with increased plasma creatine kinase levels), muscle cramps

Renal and urinary disorders:
Not known: impaired renal function including cases of renal failure in patients at risk *(see Special warnings and special precautions for use)*.

Reproductive system and breast disorders:
Uncommon: sexual dysfunction

General disorders and administration site conditions:
Common: fatigue
Uncommon: chest pain

Investigations:
Very Common: Hyperkalaemia* occurred more often in diabetic patients treated with irbesartan than with placebo. In diabetic hypertensive patients with microalbuminuria and normal renal function, hyperkalaemia (≥ 5.5 mEq/L) occurred in 29.4% of the patients in the irbesartan 300 mg group and 22% of the patients in the placebo group. In diabetic hypertensive patients with chronic renal insufficiency and overt proteinuria, hyperkalaemia (≥ 5.5 mEq/L) occurred in 46.3% of the patients in the irbesartan group and 26.3% of the patients in the placebo group.
Common: significant increases in plasma creatine kinase were commonly observed (1.7%) in irbesartan treated subjects.

None of these increases were associated with identifiable clinical musculoskeletal events.
In 1.7% of hypertensive patients with advanced diabetic renal disease treated with irbesartan, a decrease in haemoglobin*, which was not clinically significant, has been observed.
Hypoglycemia has been reported during post-marketing surveillance (see *Special warnings and special precautions for use*).

Overdose
Experience in adults exposed to doses of up to 900 mg/day for 8 weeks revealed no toxicity. The most likely manifestations of overdose are expected to be hypotension and tachycardia; bradycardia might also occur from overdose. No specific information is available on the treatment of overdose with Irbesartan. The patient should be closely monitored, and the treatment should be symptomatic and supportive. Suggested measures include induction of emesis and/or gastric lavage. Activated charcoal may be useful in the treatment of overdose. Irbesartan is not removed by haemodialysis.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties
Pharmacotherapeutic group: Angiotensin II antagonists, ATC code C09C A04.

Mechanism of action: 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.

Clinical efficacy:
Hypertension
Irbesartan lowers blood pressure with minimal change in heart rate. The decrease in blood pressure is dose-related for once a day doses with a tendency towards plateau at doses above 300 mg. Doses of 150-300 mg once daily lower supine or seated blood pressures at trough (i.e. 24 hours after dosing) by an average of 8-13/5-8 mm Hg (systolic/diastolic) greater than those associated with placebo.
Peak reduction of blood pressure is achieved within 3-6 hours after administration and the blood pressure lowering effect is maintained for at least 24 hours. At 24 hours the reduction of blood pressure was 60-70% of the corresponding peak diastolic and systolic responses at the recommended doses. Once daily dosing with 150 mg produced trough and mean 24 hour responses similar to twice daily dosing on the same total dose.
The blood pressure lowering effect of Irbesartan is evident within 1-2 weeks, with the maximal effect occurring by 4-6 weeks after start of therapy. The antihypertensive effects are maintained during long term therapy. After withdrawal of therapy, blood pressure gradually returns toward baseline. Rebound hypertension has not been observed.
The blood pressure lowering effects of irbesartan and thiazide-type diuretics are additive. In patients not adequately controlled by irbesartan alone, the addition of a low dose of hydrochlorothiazide (12.5 mg) to irbesartan once daily results in a further placebo-adjusted blood pressure reduction at trough of 7-10/3-6 mm Hg (systolic/diastolic).
The efficacy of Irbesartan is not influenced by age or gender. As is the case with other medicinal products that affect the renin-angiotensin system, black hypertensive patients have notably less response to irbesartan monotherapy. When irbesartan is administered concomitantly with a low dose of hydrochlorothiazide (e.g. 12.5 mg daily), the antihypertensive response in black patients approaches that of white patients. There is no clinically important effect on serum uric acid or urinary uric acid secretion.

Hypertension and type 2 diabetes with renal disease
The "Irbesartan Diabetic Nephropathy Trial (IDNT)" shows that irbesartan decreases the progression of renal disease in patients with chronic renal insufficiency and overt proteinuria. IDNT was a double blind, controlled, morbidity and mortality trial comparing Irbesartan, amlodipine and placebo. In 1,715 hypertensive patients with type 2 diabetes, proteinuria $\geq$ 900 mg/day and serum creatinine ranging from 1.0-3.0 mg/dl, the long-term effects (mean 2.6 years) of Irbesartan on the progression of renal disease and all-cause mortality were examined. Patients were titrated from 75 mg to a maintenance dose of 300 mg Irbesartan, from 2.5 mg to 10 mg amlodipine, or placebo as tolerated.
Patients in all treatment groups typically received between 2 and 4 antihypertensive agents (e.g., diuretics, beta blockers, alpha blockers) to reach a predefined blood pressure goal of $\leq$ 135/85 mmHg or a 10 mmHg reduction in systolic pressure if baseline was $>$ 160 mmHg. Sixty percent (60%) of patients in the placebo group reached this target blood pressure whereas this figure was 76% and 78% in the irbesartan and amlodipine groups respectively. Irbesartan significantly reduced the relative risk in the primary combined endpoint of doubling serum creatinine, end-stage renal disease (ESRD) or all-cause mortality. Approximately 33% of patients in the irbesartan group reached the primary renal composite endpoint compared to 39% and 41% in the placebo and amlodipine groups [20% relative risk reduction versus placebo (p = 0.024) and 23% relative risk reduction compared to amlodipine (p = 0.006)]. When the individual components of the primary endpoint were analysed, no effect in all cause mortality was observed, while a positive trend in the reduction in ESRD and a significant reduction in doubling of serum creatinine were observed.
Subgroups consisting of gender, race, age, duration of diabetes, baseline blood pressure, serum creatinine, and albumin excretion rate were assessed for treatment effect. In the female and black subgroups which represented 32% and 26% of the overall study population respectively, a renal benefit was not evident, although the confidence intervals do not exclude it. As for the secondary endpoint of fatal and non-fatal cardiovascular events, there was no difference among the three groups in the overall population, although an increased incidence of non-fatal MI was seen for women and a decreased incidence of non-fatal MI was seen in males in the irbesartan group versus the placebo-based regimen. An increased incidence of non-fatal MI and stroke was seen in females in the irbesartan-based regimen versus the amlodipine based regimen, while hospitalisation due to heart failure was reduced in the overall population. However, no proper explanation for these findings in women has been identified.
The study of the "Effects of Irbesartan on Microalbuminuria in Hypertensive Patients with type 2 Diabetes Mellitus (IRMA 2)" shows that irbesartan 300 mg delays progression to overt proteinuria in patients with microalbuminuria. IRMA 2 was a placebo-controlled double blind morbidity study in 590 patients with type 2 diabetes, microalbuminuria (30-300 mg/day) and normal renal function (serum creatinine $\leq$ 1.5 mg/dl in males and $<$ 1.1 mg/dl in females). The study examined the long-term effects (2 years) of Irbesartan on the progression to clinical (overt) proteinuria (urinary albumin excretion rate (UAER) $>$ 300 mg/day, and an increase in UAER of at least 30% from baseline). The pre-defined blood pressure goal was $\leq$ 135/85 mmHg. Additional antihypertensive agents (excluding ACE inhibitors, angiotensin II receptor antagonists and dihydropyridine calcium blockers) were added as needed to help achieve the blood pressure goal. While similar blood pressure was achieved in all treatment groups, fewer subjects in the irbesartan 300 mg group (5.2%) than in the placebo (14.9%) or in the irbesartan 150 mg group (9.7%) reached the endpoint of overt proteinuria, demonstrating a 70% relative risk reduction versus placebo (p = 0.0004) for the higher dose. An accompanying improvement in the glomerular filtration rate (GFR) was not observed during the first three months of treatment. The slowing in the progression to clinical proteinuria was evident as early as three months and continued over the 2 year period. Regression to normoalbuminuria ($<$ 30 mg/day) was more frequent in the Irbesartan 300 mg group (34%) than in the placebo group (21%).
Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker. ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.
These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers.
ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.
ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

Pharmacokinetic properties
Absorption
After oral administration, irbesartan is well absorbed: studies of absolute bioavailability gave values of approximately 60-80%. Concomitant food intake does not significantly influence the bioavailability of irbesartan.
Distribution
Plasma protein binding is approximately 96%, with negligible binding to cellular blood components. The volume of distribution is 53-93 litres.
Biotransformation
Following oral or intravenous administration of 14C irbesartan, 80-85% of the circulating plasma radioactivity is attributable to unchanged irbesartan. Irbesartan is metabolised by the liver via glucuronide conjugation and oxidation. The major circulating metabolite is irbesartan glucuronide (approximately 6%). In vitro studies indicate that irbesartan is primarily oxidised by the cytochrome P450 enzyme CYP2C9; isoenzyme CYP3A4 has negligible effect.
Linearity/non-linearity
Irbesartan exhibits linear and dose proportional pharmacokinetics over the dose range of 10 to 600 mg. A less than proportional increase in oral absorption at doses beyond 600 mg (twice the maximal recommended dose) was observed; the mechanism for this is unknown. Peak plasma concentrations are attained at 1.5-2 hours after oral administration. The total body and renal clearance are 157-176 and 3-3.5 ml/min, respectively. The terminal elimination half-life of irbesartan is 11-15 hours. Steady-state plasma concentrations are attained within 3 days after initiation of a once-daily dosing regimen. Limited accumulation of irbesartan ($<$ 20%) is observed in plasma upon repeated once-daily dosing. In a study, somewhat higher plasma concentrations of irbesartan were observed in female hypertensive patients. However, there was no difference in the half-life and accumulation of irbesartan. No dosage adjustment is necessary in female patients. Irbesartan AUC and Cmax values were also somewhat greater in elderly subjects ($\geq$ 65 years) than those of young subjects (18-40 years). However the terminal half-life was not significantly altered. No dosage adjustment is necessary in elderly patients.
Elimination
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.
Renal impairment
In patients with renal impairment or those undergoing haemodialysis, the pharmacokinetic parameters of irbesartan are not significantly altered. Irbesartan is not removed by haemodialysis.
Hepatic impairment
In patients with mild to moderate cirrhosis, the pharmacokinetic parameters of irbesartan are not significantly altered.
Studies have not been performed in patients with severe hepatic impairment.

Preclinical safety data
There was no evidence of abnormal systemic or target organ toxicity at clinically relevant doses. In non-clinical safety studies, high doses of irbesartan ($\geq$ 250 mg/kg/day in rats and $\geq$ 100 mg/kg/day in macaques) caused a reduction of red blood cell parameters (erythrocytes, haemoglobin, haematocrit).
At very high doses ($\geq$ 500 mg/kg/day) degenerative changes in the kidney (such as interstitial nephritis, tubular distension, basophilic tubules, increased plasma concentrations of urea and creatinine) were induced by irbesartan in the rat and the macaque and are considered secondary to the hypotensive effects of the medicinal product which led to decreased renal perfusion. Furthermore, irbesartan induced hyperplasia/hypertrophy of the juxtaglomerular cells (in rats at $\geq$ 90 mg/kg/day, in macaques at $\geq$ 10mg/kg/day). All of these changes were considered to be caused by the pharmacological action of irbesartan. For therapeutic doses of irbesartan in humans, the hyperplasia/hypertrophy of the renal juxtaglomerular cells does not appear to have any relevance.
There was no evidence of mutagenicity, clastogenicity or carcinogenicity.
Fertility and reproductive performance were not affected in studies of male and female rats even at oral doses of irbesartan causing some parental toxicity (from 50 to 650 mg/kg/day), including mortality at the highest dose. No significant effects on the number of corpora lutea, implants, or live fetuses were observed. Irbesartan did not affect survival, development, or reproduction of offspring.
Studies in animals indicate that the radiolabelled irbesartan is detected in rat and rabbit foetuses. Irbesartan is excreted in the milk of lactating rats.
Animal studies with irbesartan showed transient toxic effects (increased renal pelvic cavitation, hydroureter or subcutaneous oedema) in rat foetuses, which were resolved after birth. In rabbits, abortion or early resorption were noted at doses causing significant maternal toxicity, including mortality. No teratogenic effects were observed in the rat or rabbit.

PHARMACEUTICAL PARTICULARS

List of excipients
Microcrystalline cellulose, Carmellose calcium, Calcium stearate, Povidone k-30, Purified water, Silica colloidal anhydrous, Opadry white OY-S-38956 (HPMC 2910/Hypromellose 5cp, Talc, Titanium dioxide).

HOW SUPPLIED

Irbesartan Tablets 75 mg
Each film coated tablet contains 75 mg of Irbesartan Ph.Eur
White to off white colored, capsule shaped, biconvex, Film coated tablets, debossed with **158** on one side and H on the other side.

Irbesartan Tablets 150 mg
Each film coated tablet contains 150 mg of Irbesartan Ph.Eur
White to off white colored, capsule shaped, biconvex, Film coated tablets, debossed with **159** on one side and H on the other side.

Irbesartan Tablets 300 mg
Each film coated tablet contains 300 mg of Irbesartan Ph.Eur
White to off white colored, capsule shaped, biconvex, Film coated tablets, debossed with **160** on one side and H on the other side.

Blister pack
10's Blister pack (Alu-PVC/PvdC film)
10's Blister pack (Alu-PVC/PE/PVdC film)
"Not all presentations are marketed locally".

STORAGE
Store below 30 °C and protect from moisture.

Manufactured by:
HETERO LABS LIMITED
UNIT-V, TSIIC Formulation SEZ,
Polepally Village, Jadcherla Mandal,
Mahaboobnagar Dist., Telangana, India.

Product Owner:
HETERO LABS LIMITED
7-2-A 2, Hetero Corporate,
Industrial Estate, Sanath nagar,
Hyderabad-500018, India.