

PRODUCT INFORMATION

Abisart 75, Abisart 150, Abisart 300

Irbesartan



1. NAME OF THE MEDICINE

Irbesartan

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient in ABISART 75, ABISART 150 AND ABISART 300 (herein referred to as ABISART) tablets is irbesartan. Irbesartan is a white or almost white crystalline powder, practically insoluble in water, sparingly soluble in methanol, slightly soluble in methylene chloride

ABISART 75 contains 75 mg of irbesartan, ABISART 150 contains 150 mg of irbesartan and ABISART 300 contains 300 mg of irbesartan.

Excipient with known effect:

Each tablet of ABISART 75 mg, 150 mg, and 300 mg contains 24.70 mg, 49.40 mg and 98.80 mg of lactose monohydrate respectively. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

ABISART film coated tablets are white to off-white, film-coated, oval-shaped, biconvex and debossed with 'I3' (75 mg), 'I4' (150 mg) or 'I5' (300 mg) on one side and plain on the other. ABISART tablets are formulated for oral administration.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ABISART is indicated for the treatment of hypertension.

ABISART is indicated for delaying the progression of renal disease in hypertensive type II diabetics with persistent micro-albuminuria (≥ 30 mg per 24 hours) or urinary protein in excess of 900 mg per 24 hours.

4.2 DOSE AND METHOD OF ADMINISTRATION

ABISART may be used either alone or in combination with other antihypertensive agents (e.g., thiazide diuretic, beta-adrenergic blocking agent, long-acting calcium-channel blocking agent).

The usual initial and maintenance dose of ABISART is 150 mg once daily. ABISART may be administered with or without food. Therapy should be adjusted according to blood pressure response. Patients requiring further reduction in blood pressure should have the dose increased to 300 mg once daily.

In patients with hypertension and type II diabetic renal disease 300 mg of irbesartan once daily is the preferred maintenance dose. Although irbesartan slowed the progression of renal disease in hypertensive patients separately to its effect on blood pressure, this does not remove the clinical requirement for a patient's blood pressure to be adequately controlled. If irbesartan alone is insufficient, then other agents should be added in order to gain blood pressure control.

Irbesartan increases the risk of significant hyperkalaemia in hypertensive patients with type II diabetes and moderate to severe renal insufficiency (see Section 4.4 SPECIAL WARNING AND PRECAUTIONS FOR USE – Effects on Laboratory Tests, Hyperkalaemia.). Serum potassium should be monitored regularly in such patients.

If blood pressure is not adequately controlled with irbesartan alone, a diuretic (e.g., hydrochlorothiazide 12.5 mg daily) or another antihypertensive drug (e.g., beta-adrenergic blocking agent, long-acting calcium channel blocking agent) may be added.

Patients with Intravascular Volume Depletion

Volume and/or sodium-depletion should be corrected before initiating therapy with irbesartan or a lower starting dose (e.g. 75 mg) should be considered. Patients undergoing haemodialysis should receive a starting dose of 75 mg and the dose should be adjusted according to B.P. response. If the blood pressure is not adequately controlled, the dose can be increased.

Elderly and Patients with Renal or Hepatic Impairment

No dosage reduction is generally necessary in the elderly or in patients with impaired hepatic function (mild to moderate degree) or impaired renal function (regardless of degree), unless accompanied by uncorrected volume depletion (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION - Patients with Intravascular Volume Depletion, above).

4.3 CONTRAINDICATIONS

ABISART is contraindicated in patients who are hypersensitive to irbesartan or to any other component of the irbesartan formulation.

Do not co-administer ABISART with aliskiren-containing medicines in patients with diabetes or with moderate to severe renal impairment.

Pregnancy – see Section 4.6 FERTILITY, PREGNANCY AND LACTATION – Use in pregnancy.

4.4 SPECIAL WARNING AND PRECAUTIONS FOR USE

This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose- galactose malabsorption should not take this medicine.

Hypotension – Volume-Depleted Patients

Irbesartan has been rarely associated with hypotension in hypertensive patients without other co-morbid conditions. Symptomatic hypotension, as with ACE inhibitors, may be expected to occur in sodium/volume depleted patients such as those treated vigorously with diuretics and/or salt restriction, or on haemodialysis. Volume and/or sodium- depletion should be corrected before initiating therapy with irbesartan or a lower starting dose (e.g. 75 mg) should be considered. Patients undergoing haemodialysis should receive a starting dose of 75 mg and the dose should be adjusted according to B.P. response.

Hyperkalaemia

While hyperkalaemia in uncomplicated patients with hypertension has not been reported with irbesartan, hyperkalaemia may occur during treatment with other drugs that affect the renin-angiotensin-aldosterone system, especially in the presence of renal impairment and/or heart failure. Adequate monitoring of serum potassium in patients at risk is recommended.

Dual blockade of the Renin-Angiotensin-Aldosterone System (RAAS) with aliskiren containing medicinal products

Dual blockade of the RAAS by combining irbesartan with aliskiren is not recommended since there is an increased risk of hypotension, hyperkalemia, and changes in renal function. The use of irbesartan in combination with aliskiren is contraindicated in patient with diabetes mellitus or renal impairment (see Section 4.3 CONTRAINDICATIONS).

Cardiac Disorders

The safety of irbesartan in the presence of heart failure has not been fully defined. Sudden death has occurred in some studies of patients with heart failure, and although such deaths may have reflected the natural history of the underlying heart failure, caution is recommended when treating such patients with irbesartan.

At this time, experience is limited with irbesartan in the treatment of patients with ventricular dysfunction or cardiac arrhythmias; caution is advised.

Use in renal impairment

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 depends on the activity of the renin-angiotensin-aldosterone system (e.g., hypertensive patients with renal artery stenosis in one or both kidneys, or patients with severe congestive heart failure), treatment with drugs that affect this system has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. The possibility of a similar effect occurring with the use of an angiotensin II receptor antagonist, including irbesartan cannot be excluded.

In hypertensive type II diabetic patients with proteinuria (≥ 900 mg/day), a population which has a high risk of renal artery stenosis, no patient treated with irbesartan in IDNT had an early acute rise in serum creatinine attributable to renal artery disease (see Section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials).

Experience is limited with irbesartan in patients with moderate to severe renal impairment; careful monitoring of renal function and potassium in such patients is advised.

Use in the elderly

Among patients who received irbesartan in clinical studies, no overall differences in efficacy or safety were observed between older patients (65 years or older) and younger patients.

Paediatric use

Safety and effectiveness in paediatric patients have not been established.

Effects on Laboratory Tests

No clinically significant changes in laboratory test parameters occurred in controlled clinical studies of hypertension. No special monitoring of laboratory parameters is necessary for patients with uncomplicated essential hypertension. Monitoring of potassium levels and renal function is recommended for patients with heart failure and those with moderate to severe renal impairment (see Section 4.4 SPECIAL WARNING AND PRECAUTIONS FOR USE).

In two clinical studies of patients with hypertension and type II diabetic renal disease (IDNT and IRMA2) the following was reported.

Hyperkalaemia: In IDNT the percent of subjects with hyperkalaemia (> 6 mmol/L) was 18.6% in the irbesartan group compared to 6.0% in the placebo group. In IRMA 2 the percent of subjects with

hyperkalaemia (> 6 mmol/L) was 1.0% in the irbesartan groups and none in the placebo group. In IDNT discontinuations due to hyperkalaemia in the irbesartan group were 2.1% vs 0.36% in the placebo group. In IRMA 2 discontinuations due to hyperkalaemia in the irbesartan groups were 0.5% vs none in the placebo group.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Based on in vitro data, no interactions would be expected to occur with drugs whose metabolism is dependent upon cytochrome P450 isoenzymes CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2D6, CYP2E1 or CYP3A4. Irbesartan is primarily metabolised by CYP2C9, however, during clinical interaction studies, no significant pharmacodynamic interactions were observed when irbesartan was co-administered with warfarin (a drug metabolised by CYP2C9).

Irbesartan does not affect the pharmacokinetics of digoxin. The pharmacokinetics of irbesartan is not affected by coadministration with nifedipine or hydrochlorothiazide.

Potassium-sparing diuretics, potassium supplements, potassium containing salt substitutes

Based on experience with the use of other drugs that affect the renin-angiotensin system, concomitant use of potassium-sparing diuretics, potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium.

Lithium

Reversible increases in lithium concentrations have been very rarely reported with irbesartan. Therefore, if coadministration of irbesartan and lithium proves necessary, careful monitoring of serum lithium levels is necessary.

Combination use of ACE inhibitors or angiotensin receptor antagonists, anti-inflammatory drugs and thiazide diuretics

Concomitant use of a renin-angiotensin system inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist), and an anti-inflammatory drug (NSAID, including COX-2 inhibitor) alone or with a thiazide diuretic may increase the risk of renal impairment, including possible acute renal failure. These effects are usually reversible. This includes use in fixed-combination products containing more than one class of drug. The combination of these agents should be administered with caution, especially in the elderly, volume-depleted, and in patients with pre-existing renal impairment. Renal function (serum creatinine) should be monitored after initiation of concomitant therapy, and periodically thereafter. The antihypertensive effect of angiotensin II receptor antagonists, including irbesartan, may be attenuated by NSAIDs including selective COX-2 inhibitors.

Renin inhibitor

The combination of irbesartan with aliskiren-containing medicinal products is contraindicated in patients with diabetes mellitus or moderate to severe renal impairment and is not recommended in other patients (see Section 4.3 CONTRAINDICATIONS).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Fertility and reproductive performance were not affected in studies of male and female rats at oral doses of up to 650 mg/kg/day (approximately 3 (male) and 8 (female) fold higher exposure, based on AUC, than that of humans at the maximum recommended clinical dose of 300 mg/day).

Use in pregnancy (Category D)

Drugs that act directly on the renin-angiotensin system can cause foetal 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, irbesartan 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 have been associated with foetal 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 foetal renal function; oligohydramnios in this setting has been associated with foetal 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 foetuses 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 irbesartan as soon as possible.

Infants with histories of in utero exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria and hyperkalaemia.

When pregnant rats were treated with irbesartan from day 0 to day 20 of gestation, at doses of 50 mg/kg/day and higher, transient effects (increased renal pelvic cavitation, hypoureter or subcutaneous oedema) were noted in full term rat foetuses but not in the young animals necropsied after 6 weeks of age. In pregnant rabbits, at doses of 30 mg/kg/day, maternal mortality, abortion and early foetal resorptions were noted. No teratogenic effects were observed in the rat or rabbit.

Use in lactation

Irbesartan is excreted in the milk of lactating rats. It is not known whether irbesartan or its metabolites are excreted in human milk. A decision should be made whether to discontinue breast feeding or to discontinue the drug, taking into account the importance of irbesartan to the therapy of the mother and the potential risk to the infant.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effect of irbesartan on ability to drive and use machines has not been studied. When driving vehicles or operating machines, it should be taken into account that occasionally dizziness or weariness may occur during treatment of hypertension.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Hypertension

Irbesartan has been evaluated for safety in approximately 5000 subjects in clinical studies, including 1300 hypertensive patients treated for over 6 months and over 400 patients treated for one year or more. Adverse events in patients receiving irbesartan were generally mild and transient with no relationship to dose. The incidence of adverse events was not related to age, gender, or race.

Table: Clinical Adverse Events* in Placebo-Controlled Hypertension Trials

BODY SYSTEM/EVENT	Incidence	
	Percentage (%) of Patients*	
	Irbesartan n=1965	Placebo n=641
General		
Fatigue	4.3	3.7
Influenza	2.3	2.0
Chest pain	1.8	1.7
Cardiovascular		
Oedema	1.5	2.3
Tachycardia	1.2	0.9
Gastrointestinal		
Diarrhoea	3.1	2.2
Nausea/Vomiting	2.1	2.8
Dyspepsia/Heartburn	1.7	1.1
Abdominal Pain	1.4	2.0
Nervous System		
Dizziness	4.9	5.0
Headache ^a	12.3	16.7
Anxiety/Nervousness	1.1	0.9
Dermatological		
Rash	1.3	2.0
Musculoskeletal/Connective		
Musc/Skel Pain	6.6	6.6
Musc/Skel Trauma ^a	1.9	0.5
Renal/Genitourinary		
UTI	1.1	1.4
Respiratory		
Upper Resp. Infection	8.5	6.2
Sinus Abnormality	3.4	5.0
Cough	2.8	2.7
Pharyngitis	2.2	2.5
Rhinitis	1.9	2.8

^a Statistically significant difference between irbesartan and placebo treatment groups.

In placebo-controlled clinical studies, including 1965 irbesartan-treated patients (usual duration of treatment 1 to 3 months), discontinuations due to any clinical or laboratory adverse event were 3.3 percent for irbesartan-treated patients and 4.5 percent for placebo-treated patients (p=0.029).

Clinical adverse events, occurring in at least 1% of patients treated with irbesartan in placebo controlled trials are shown in the table below. The incidence of the same adverse events in the placebo control group is also shown.

Adverse reactions that occurred in 2 or more hypertensive patients in clinical trials involving 3396 patients have been classified using standard terminology and in the following listing are categorised by body system and listed in order of decreasing frequency according to the following definitions: common adverse reactions are those occurring on one or more occasions in at least 1/100 but less than 1/10 patients; uncommon adverse reactions are those occurring in at least 1/1000 but less than 1/100 patients; rare adverse reactions are those occurring in less than 1/1000 patients.

Cardiovascular: *Uncommon*: subjective rhythm disturbance, flushing, ECG abnormality, cardiac murmur, cardiac rhythm disturbance, orthostatic hypotension, atrial rhythm disturbance, bradycardia, hypotension; *Rare*: syncope, conduction disorder, myocardial infarction.

Dermatologic: *Uncommon*: pruritus, facial erythema; *Rare*: dermatitis, acne, scalp-hair abnormality.

Endocrine/Metabolic/Electrolyte Imbalance: *Uncommon*: sexual dysfunction, libido change; *Rare*: breast disorder, gout, hot flashes

Gastrointestinal: *Uncommon*: constipation, flatulence, dry mouth, abdomen distention; *Rare*: abnormal stool, decreased appetite, increased appetite, oral lesion, dysphagia, oesophagitis.

General: *Uncommon*: weakness, hyperhidrosis, malaise, weight gain; *Rare*: cold sensation, warmth sensation, pain.

Hematopoietic: *Rare*: anaemia.

Immunology/Sensitivity Disorder: *Uncommon*: upper extremity oedema; *Rare*: head/neck oedema.

Musculoskeletal/Connective Tissue: *Uncommon*: muscle cramp, swelling extremity; *Rare*: arthritis, muscle ache, myalgia, extremity weakness, stiffness lower extremity.

Nervous System: *Uncommon*: orthostatic dizziness, numbness, sleep disturbance, depression, emotion labile/disturbance, somnolence, vertigo, paresthesia; *Rare*: stress related disorder, tremor, coordination disturbance, disturbing dreams.

Renal/Genitourinary: *Uncommon*: urination abnormality.

Respiratory: *Uncommon*: epistaxis, dyspnoea.

Special Senses: *Uncommon*: vision disturbance, hearing abnormality; *Rare*: eye disturbance - other, eyelid abnormality, visual field abnormality, medication bad taste, taste disturbance.

Hypertension and Type II Diabetic Renal Disease

In clinical studies (see Section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials, Hypertension and type II diabetic renal disease), the adverse experiences were similar to those in clinical trials of hypertensive patients with the exception of orthostatic symptoms (dizziness, orthostatic dizziness and orthostatic hypotension) observed in IDNT (proteinuria \geq 900mg/day, and serum creatinine from 90 - 265 μ mol/L). In IDNT 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%). The rates (percents) of discontinuations due to orthostatic symptoms for irbesartan versus placebo were: dizziness 0.3 vs 0.5; orthostatic dizziness 0.2 vs 0.0; and orthostatic hypotension, 0.0 vs 0.0.

Postmarketing Experience

As with other angiotensin-II receptor antagonists, rare cases of hypersensitivity reactions (urticaria, angioedema) have been reported since the marketing of irbesartan. The following have been reported during post-marketing surveillance: vertigo, asthenia, hyperkalaemia, myalgia, jaundice, elevated liver function tests, hepatitis, arthralgia, tinnitus and impaired renal function including cases of renal failure in patients at risk (see Section 4.4. SPECIAL WARNING AND PRECAUTIONS FOR USE).

Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at <http://www.tga.gov.au/reporting-problems>.

4.9 OVERDOSE

Experience in adults exposed to doses of up to 900 mg/day for 8 weeks revealed no toxicity. No specific information is available on the treatment of overdosage with irbesartan. The patient should be closely monitored, and the treatment should be symptomatic and supportive. If simple supine positioning is found insufficient to correct hypotension then judicious I.V. volume replacement / augmentation may be indicated. Irbesartan is not removed from the body by haemodialysis.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Irbesartan is a specific antagonist of angiotensin II receptors (AT1 subtype). Angiotensin II is an important component of the renin-angiotensin system and is involved in the pathophysiology of hypertension and in sodium homeostasis. Irbesartan does not require metabolic activation for its activity.

Irbesartan blocks the potent vasoconstrictor and aldosterone-secreting effects of angiotensin II by selective antagonism of the angiotensin II (AT1 subtype) receptors localised on vascular smooth muscle cells and in the adrenal cortex. It has no agonist activity at the AT1 receptor and a much greater affinity (more than 8500-fold) for the AT1 receptor than for the AT2 receptor (a receptor that has not been shown to be associated with cardiovascular homeostasis).

Irbesartan does not inhibit enzymes involved in the renin-angiotensin system (i.e., renin, angiotensin converting enzyme [ACE]) or affect other hormone receptors or ion channels involved in the cardiovascular regulation of blood pressure and sodium homeostasis.

In healthy subjects, single oral irbesartan doses of up to 300 mg produced dose-dependent inhibition of the pressor effect of angiotensin II infusions. Inhibition was complete ($\geq 90\%$) at the time of peak irbesartan concentrations and sustained for 24 hours (60% and 40% at 300 mg and 150 mg, respectively).

In hypertensive patients, angiotensin II receptor inhibition following chronic administration of irbesartan causes a 1.5-2 fold rise in angiotensin II plasma concentration and a 2-3 fold increase in plasma renin levels. Aldosterone plasma concentrations generally decline following irbesartan administration, however serum potassium levels are not significantly affected at recommended doses.

In hypertensive patients, chronic oral doses of irbesartan (up to 300 mg) had no effect on glomerular filtration rate, renal plasma/blood flow or filtration fraction. In multiple dose studies in hypertensive patients, there were no notable effects on fasting triglycerides, total cholesterol or HDL-cholesterol or fasting glucose concentrations. There was no effect on serum uric acid during chronic oral administration. Following repeated doses of irbesartan, there was no uricosuric effect.

Clinical trials

The antihypertensive effects of irbesartan were examined in seven (7) major placebo-controlled 8-12 week trials in patients with baseline diastolic blood pressures of 95-110 mmHg.

The seven (7) studies of irbesartan monotherapy included a total of 1915 patients randomised to irbesartan (1-900 mg) and 611 patients randomised to placebo. Once daily doses of 150 to 900 mg provided statistically and clinically significant decreases in systolic and diastolic blood pressure with a plateau in effect at doses above 300 mg.

Systolic/diastolic mean decreases in blood pressure at trough (24 hours post-dosing), compared to placebo, following 6 to 12 weeks of treatment were in the range of 7.5-9.9/4.6-6.2 mmHg with a 150 mg dose, and 7.9-12.6/5.2-7.9 mmHg with a 300 mg dose.

Once-daily dosing with 150 mg gave trough and mean 24 hour responses corresponding to those observed in patients receiving twice-daily dosing at the same total daily dose. Peak (3-6 hour) effects were uniformly, but moderately, larger than trough effects, with the trough-to-peak ratio for systolic and diastolic response generally between 60-70%. Two of the seven placebo-controlled trials identified above and two additional studies examined the antihypertensive effects of irbesartan and hydrochlorothiazide in combination.

Addition of a low dose of hydrochlorothiazide (12.5 mg) to irbesartan (75 to 300 mg) once daily resulted in further diastolic blood pressure reductions at trough (24 hours post-dosing) of 2.3-4.8 mmHg and an overall systolic/diastolic placebo-subtracted reduction of up to 13.6/11.5 mmHg at a dose of 300 mg irbesartan and 12.5 mg hydrochlorothiazide. Once daily dosing with 150 mg irbesartan and 12.5 mg hydrochlorothiazide gave systolic/diastolic mean placebo-adjusted blood pressure reductions at trough (24 hours post-dosing) of 12.9/6.9 mmHg.

In patients not adequately controlled ($\text{SeDBP} \geq 90$ mmHg) on irbesartan (up to 300 mg) alone, the addition of 12.5 mg hydrochlorothiazide gave an added reduction of up to 6.1 mmHg in trough (24 hours) diastolic blood pressure.

In patients not adequately controlled (SeDBP 93-120 mmHg) on 25 mg hydrochlorothiazide alone, the addition of irbesartan (75-150 mg) gave an added systolic/diastolic mean reduction of 11.1/7.2 mmHg.

Analysis of age, gender and race subgroups of patients showed that men and women, and patients over and under 65 years of age, had generally similar responses.

The effect of irbesartan is apparent after the first dose, substantially present within 1-2 weeks, and reaches a maximal effect within 4-6 weeks. In long-term studies the effect of irbesartan appeared to be maintained for more than one year. After withdrawal of irbesartan, blood pressure gradually returned towards baseline; no rebound was observed. There was essentially no change in average heart rate in irbesartan-treated patients in controlled trials.

Hypertension and type II diabetic renal disease

The Irbesartan Diabetic Nephropathy Trial (IDNT) was a multicentre, randomised, controlled, double-blind, morbidity and mortality trial comparing irbesartan, amlodipine and placebo. In 1715 hypertensive patients with type II diabetes (proteinuria ≥ 900 mg/day and serum creatinine 110-265 $\mu\text{mol/L}$ in men and 90-265 $\mu\text{mol/L}$ in women) the long-term effects (mean 2.6 years) of irbesartan on the progression of renal disease and all-cause mortality were examined. In addition, a secondary end-point, the effect of irbesartan on the risk of fatal or non-fatal cardiovascular events was assessed. Patients were randomised to receive irbesartan

75 mg, amlodipine 2.5 mg, or matching placebo once-daily. Patients were then titrated to a maintenance dose of 300 mg irbesartan, 10 mg amlodipine, or placebo as tolerated. Additional antihypertensive agents (excluding ACE inhibitors, angiotensin II receptor antagonists and calcium channel blockers) were added as needed to help achieve blood pressure goal ($\leq 135/85$ or 10 mmHg reduction in systolic blood pressure if higher than 160 mmHg) for patients in all groups. Irbesartan demonstrated a 20% relative risk reduction in the composite primary endpoint (first occurrence of any of the following: doubling of serum creatinine, end-stage renal disease or all-cause mortality) compared to placebo (95% CI (3%, 34%), $p = 0.023$) and a 23% relative risk reduction compared to amlodipine (95% CI (7%, 37%), $p = 0.006$).

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. Similar blood pressure was achieved in the irbesartan and amlodipine groups. There was no significant difference in the assessment of fatal or non-fatal cardiovascular events (cardiovascular death, non-fatal myocardial infarction, hospitalisation for heart failure, permanent neurologic deficit attributed to stroke, or above-the-ankle amputation) among the three treatment groups.

The study of the Effects of Irbesartan on MicroAlbuminuria in Hypertensive Patients with Type 2 Diabetes Mellitus (IRMA 2) was a multicentre, randomised, placebo-controlled, double-blind morbidity study, conducted in 590 hypertensive patients with type II diabetes, microalbuminuria (20 – 200 mcg/min; 30 –300 mg/day) and normal renal function (serum creatinine $\leq 130 \mu\text{mol/L}$ in males and $\leq 100 \mu\text{mol/L}$ in females). The study examined as a primary endpoint the long-term effects (2 years) of irbesartan on the progression to (overt) proteinuria (urinary albumin excretion rate [AER] $> 200 \mu\text{g/min}$ [$>$ approximately 300 mg/day] and an increase in AER of at least 30% from baseline). In addition, after one and two years of treatment, the effect of irbesartan on the change in overnight AER and the change in 24-hour creatinine clearance was assessed. Patients were randomised to receive irbesartan 150 mg, irbesartan 300 mg, or matching placebo once daily. Additional antihypertensive agents (excluding ACE inhibitors, angiotensin II receptor antagonists and dihydropyridine calcium blockers) were added as needed to help achieve blood pressure goal ($\leq 135/85$ mmHg) for patients in all groups. Irbesartan 300 mg demonstrated a 70% relative risk reduction in the development of clinical (overt) proteinuria compared to placebo (95% CI (39%, 86%), $p = 0.0004$). Irbesartan 150 mg demonstrated a 39% relative risk reduction in the development of proteinuria compared to placebo (95% CI (-8%, 66%), $p = 0.085$). In the intent to treat analysis, when the primary endpoint is adjusted for urinary albumin excretion rate and mean arterial pressure, irbesartan 300 mg demonstrated a 68% relative risk reduction, (95% CI (35%, 85%), $p = 0.002$). The slowing of progression to clinical (overt) proteinuria was evident as early as three months and continued over the 2 year period. The decline in 24-hour creatinine clearance did not differ significantly among the 3 groups. Regression to normoalbuminuria ($< 20 \mu\text{g/min}$; $< 30 \text{mg/day}$) was more frequent in the irbesartan 300 mg group (34%) than in the placebo group (21%).

The adverse experiences reported in these two studies are summarised under Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) - Hypertension and Type II Diabetic Renal Disease and Section 4.4 SPECIAL WARNING AND PRECAUTIONS FOR USE – Effects on Laboratory Tests.

5.2 PHARMACOKINETIC PROPERTIES

Irbesartan is an orally active agent and does not require biotransformation for its activity.

Absorption

Following oral administration, irbesartan is rapidly and well absorbed. In studies employing an injection and an oral solution containing radio-labelled irbesartan, the average absolute oral bioavailability of irbesartan was 60- 80%. Median peak plasma concentrations generally occurred 1.5 -2 hours after oral administration of irbesartan capsules and tablets. Food did not affect the bioavailability.

Distribution

Irbesartan is 90% protein-bound in the plasma, and has negligible binding to cellular components of blood. The volume of distribution (V_{ss}) is 53-93 L.

Metabolism

Following oral or intravenous administration of ¹⁴C irbesartan more than 80% of the circulating plasma radioactivity was attributable to unchanged irbesartan. Irbesartan is metabolised by the liver via glucuronide conjugation and oxidation. The major circulating metabolite is irbesartan glucuronide (~6%).

Irbesartan undergoes oxidation primarily by the cytochrome P450 isoenzyme CYP2C9; isoenzyme CYP3A4 has negligible effect. It is not metabolised by, nor does it substantially induce or inhibit most isoenzymes commonly associated with drug metabolism (i.e., CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2D6, or CYP2E1). Irbesartan does not induce nor inhibit isoenzyme CYP3A4.

Excretion

Irbesartan and its metabolites are excreted by both biliary and renal routes. About 20% of the administered radioactivity after an oral or intravenous dose of ¹⁴C irbesartan was recovered in urine with the remainder in the faeces. Less than 2% of the dose was excreted in urine as unchanged irbesartan.

The terminal elimination half-life ($t_{1/2}$) of irbesartan averaged 11-15 hours over a range of doses following multiple oral dosing. The total body clearance of intravenously administered irbesartan was 157-176 mL/min, of which 3.0-3.5 mL/min was renal clearance. Irbesartan exhibits linear pharmacokinetics over the therapeutic dose range. Steady-state plasma concentrations are attained within 3 days after initiation of a once-daily dosing regimen. Limited accumulation (< 20%) is observed in plasma upon repeated once-daily dosing.

Special Populations

In male and female hypertensive subjects, higher (11-44%) plasma concentrations of irbesartan were observed in females than in males, although, following multiple dosing, males and females did not show differences in either accumulation or elimination half-life. No gender-specific differences in clinical effect have been observed.

In elderly (male and female) normotensive subjects (65-80 years) with clinically normal renal and hepatic function, the plasma AUC and peak plasma concentrations (C_{max}) of irbesartan are approximately 20%-50% greater than those observed in younger subjects (18-40 years). Regardless of age, the elimination half-life is comparable. No significant age-related differences in clinical effect have been observed.

In black and white normotensive subjects, the plasma AUC and $t_{1/2}$ of irbesartan are approximately 20-25% greater in blacks than in whites; the peak plasma concentrations (C_{max}) of irbesartan are essentially equivalent.

In patients with renal impairment (regardless of degree) and in haemodialysis patients, the pharmacokinetics of irbesartan are not significantly altered. Irbesartan is not removed by haemodialysis.

In patients with hepatic insufficiency due to mild to moderate cirrhosis, the pharmacokinetics of irbesartan are not significantly altered.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Irbesartan was not genotoxic in a series of assays for mutagenic and clastogenic effects.

Carcinogenicity

The carcinogenic potential of irbesartan was assessed in two 104 week studies in mice and rats. No carcinogenic potential was observed in either species at doses of up to 500 mg/kg/day (male rats) and 1000 mg/kg/day (mice and female rats). The AUC based exposure levels were 3-6 fold higher in mice, 3 fold

higher in male rats and 25 fold higher in female rats than that of humans at the maximum recommended clinical dose of 300 mg/day.

6 PHARMACEUTICAL PROPERTIES

6.1 LIST OF EXCIPIENTS

- lactose monohydrate
- microcrystalline cellulose
- croscarmellose sodium
- hypromellose
- colloidal anhydrous silica
- magnesium stearate
- Opadry II OY-LS-28900 White (Proprietary Ingredient No.107728)

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

The tablets are available in blister (PVC/PE/PVDC/Al or PVC/PCTFE(Aclar)/Al) packs of 30 and 90.

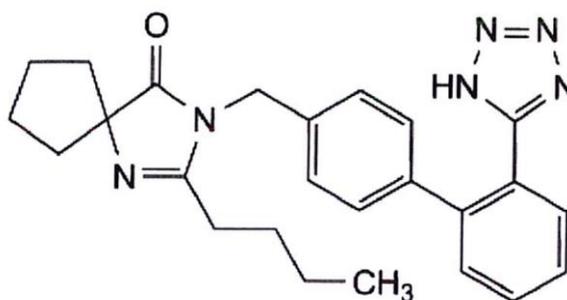
Some strengths, pack sizes and/or pack types may not be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSIOCHEMICAL PROPERTIES

Chemical name: 2-Butyl-3-[[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1,3-diazaspiro[4.4]non-1-en-4-one

Chemical structure:

Molecular formula: C₂₅H₂₈N₆O

Molecular weight: 428.5

CAS number: 138402-11-6

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

30/10/2018

10 DATE OF REVISION

25/10/2018

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information

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