AUSTRALIAN PRODUCT INFORMATION
KARVEZIDE® (IRBESARTAN/HYDROCHLOROTHIAZIDE)

1 NAME OF THE MEDICINE

Irbesartan/hydrochlorothiazide

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Karvezide 150/12.5 tablets contain 150 mg of irbesartan and 12.5 mg of hydrochlorothiazide.

Karvezide 300/12.5 tablets contain 300 mg of irbesartan and 12.5 mg of hydrochlorothiazide.

Karvezide 300/25 tablets contain 300 mg of irbesartan and 25 mg of hydrochlorothiazide.

Excipients with known effect:

Lactose monohydrate.

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

3 PHARMACEUTICAL FORM

Karvezide 150/12.5 tablets are peach to mottled peach coloured, biconvex, oval-shaped, film-coated tablets debossed with a heart on one side and the number “2875” on the other side.

Karvezide 300/12.5 tablets are peach to mottled peach coloured, biconvex, oval-shaped, film-coated tablets debossed with a heart on one side and the number “2876” on the other side.

Karvezide 300/25 tablets are pink, biconvex, oval-shaped, film-coated tablets debossed with a heart on one side and the number “2788” on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Karvezide is indicated for the treatment of hypertension. Treatment should not be initiated with this fixed dose combination.

4.2 DOSE AND METHOD OF ADMINISTRATION

Karvezide should not be initiated as first-line therapy. The daily dose can be administered with or without food.

Replacement Therapy

The combination may be substituted for the titrated components.

Dose Titration by Clinical Effect

When clinically appropriate, direct change from monotherapy to the fixed combinations may be considered:

- Karvezide 150/12.5 mg may be administered to patients whose blood pressure is not adequately controlled with hydrochlorothiazide or irbesartan 150 mg alone.
- Karvezide 300/12.5 mg may be administered to patients insufficiently controlled by irbesartan 300 mg or by Karvezide 150/12.5 mg.
- Karvezide 300/25 mg may be administered to patients insufficiently controlled by Karvezide 300/12.5 mg.

Doses higher than 300 mg irbesartan/25 mg hydrochlorothiazide once daily are not recommended. When necessary, Karvezide may be administered with another antihypertensive drug.

Patients with Intravascular Volume Depletion

In severely volume-depleted and/or sodium-depleted patients, such as those treated vigorously with diuretics, the condition should be corrected prior to administration of Karvezide.

Elderly Patients

No dosage reduction is generally necessary for daily dosage of irbesartan 150 mg/ hydrochlorothiazide 12.5 mg in the elderly.

Patients with Renal Impairment

No dosage reduction is generally necessary for daily dosage of irbesartan 150 mg/hydrochlorothiazide 12.5 mg in patients with mild to moderate renal impairment (creatinine clearance > 30 mL/min).

Patients with Hepatic Impairment

No dosage reduction is thought to be necessary in patients with mild to moderate hepatic impairment as the pharmacokinetics of neither irbesartan nor hydrochlorothiazide are affected by hepatic impairment. Due to the hydrochlorothiazide component, Karvezide should be used with caution in patients with severe hepatic impairment (see Section 4.4 Special warnings and precautions for use).

4.3 CONTRAINDICATIONS

Karvezide is contraindicated in patients who are hypersensitive to irbesartan, sulphonamide derived drugs (e.g. thiazides), or to any other component of the Karvezide formulation. In general, hypersensitivity reactions are more likely to occur in patients with a history of allergy or bronchial asthma.

Karvezide is contraindicated in patients who are anuric.

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

Do not co-administer Karvezide with ACE inhibitors in patients with diabetic nephropathy.

Pregnancy. (See Section 4.6 Fertility, pregnancy and lactation)

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Non-melanoma Skin Cancer

An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies based on Danish National Cancer Registry (see Section 5.1 Pharmacodynamic Properties). Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC.

Patients taking HCTZ should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions.

Possible preventive measures such as limited exposure to sunlight and ultraviolet (UV) rays and, in case of exposure, adequate protection should be advised to the patients in order to minimise the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of HCTZ may also need to be reconsidered in patients who have experienced previous non-melanoma skin cancer (see Section 4.8 Adverse effects (Undesirable effects)).

Hypotension - Volume - Depleted Patients

Karvezide has been rarely associated with hypotension in hypertensive patients without other risk factors for hypotension. Symptomatic hypotension may be expected to occur in patients who have been sodium and/or volume depleted by vigorous diuretic therapy and/or dietary salt restriction, or vomiting and/or diarrhoea or haemodialysis. Volume and/or sodium-depletion should be corrected before initiating therapy with Karvezide. Thiazides may potentiate the action of other antihypertensive drugs (see Section 4.5 Interactions with other medicines and other forms of interactions).

Renal Impairment

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function during therapy with Karvezide 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 azotaemia 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 Karvezide, cannot be excluded.

There is no experience with Karvezide in patients with a recent renal transplant.

Karvezide is not recommended for patients with severe renal disease (creatinine clearance ≤ 30 mL/min) (see Section 4.3 Contraindications). Hydrochlorothiazide-associated precipitation of azotemia may occur in patients with impaired renal function. As experience is limited in patients with a creatinine clearance >30 and <60mL/min, Karvezide should be administered with caution to such patients.

Hyperkalaemia

Concomitant use of irbesartan with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicinal products which may increase the potassium level (eg trimethoprim containing medicines) may lead to an increase in serum potassium and should therefore be co-administered cautiously with irbesartan.

Dual blockade of the Renin-Angiotensin-Aldosterone System (RAAS)

Dual blockade of the RAAS by combining Karvezide with an ACE inhibitor or with aliskiren is not recommended since there are increased risks of hypotension, hyperkalaemia, and changes in renal function. The use of Karvezide in combination with aliskiren is contraindicated in patient with diabetes mellitus or renal impairment (see Section 4.3 Contraindications).

The use of Karvezide in combination with aliskiren is contraindicated in patients with diabetes mellitus or with moderate to severe renal impairment.

The use of Karvezide in combination with an ACE inhibitor is contraindicated in patients with diabetic nephropathy (See Section 4.3 Contraindications and Section 4.5 Interactions with other medicines and other forms of interactions).

Psoriasis

The use of Karvezide in patients with psoriasis or a history of psoriasis should be carefully weighed as it may exacerbate psoriasis.

Renal Artery Stenosis

See comments under Renal Impairment above.

Primary Aldosteronism

Patients with primary aldosteronism generally will not respond to antihypertensive medicines acting through inhibition of the renin-angiotensin system. Therefore the use of Karvezide is not recommended.

Postsympathectomy

The antihypertensive effects of thiazide diuretics may be increased in the postsympathectomy patient.

Fluid and Electrolyte Imbalance

Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (hypokalaemia, hyponatraemia and hypochloraemic alkalosis). Although hypokalaemia may

develop when thiazide diuretics are used alone, especially with higher doses, concurrent therapy with irbesartan reduces the frequency of diuretic-induced hypokalaemia. Chloride deficit is generally mild and usually does not require treatment. Calcium excretion is decreased by thiazides which may cause intermittent and slight elevation of serum calcium. Marked hypercalcaemia suggests the possibility of hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function. Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia.

Monitoring of laboratory parameters may be necessary in patients at risk of electrolyte imbalance.

Metabolic and Endocrine Effects

Hyperuricaemia may occur, and an acute attack of gout may be precipitated in certain patients receiving thiazide therapy. Insulin requirements in diabetic patients may be increased and latent diabetes mellitus may become manifest during thiazide administration. Increases in cholesterol and triglyceride levels have been associated with thiazide diuretic therapy, however, minimal or no effects were reported at the 12.5 mg hydrochlorothiazide dose contained in Karvezide.

Monitoring of laboratory parameters may be necessary in patients at risk of metabolic disturbances.

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 4.8 Adverse effects (undesirable effects).

Systemic Lupus Erythematosus

Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazide diuretics.

Acute Respiratory Toxicity

Severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS) have been reported after taking hydrochlorothiazide. Pulmonary oedema typically develops within minutes to hours after hydrochlorothiazide intake. At the onset, symptoms include dyspnoea, fever, pulmonary deterioration and hypotension. If diagnosis of ARDS is suspected, Karvezide should be withdrawn and appropriate treatment should be given. Hydrochlorothiazide must not be administered to patients who previously experienced ARDS following intake of hydrochlorothiazide or another thiazide diuretic.

Choroidal Effusion, Secondary Acute Angle-Closure Glaucoma and/or Acute Myopia

Hydrochlorothiazide is a sulfonamide. Sulfonamide, or sulfonamide derivative drugs can cause an idiosyncratic reaction, which may result in choroidal effusion with visual field defect, secondary acute angle-closure glaucoma and/or acute myopia. Isolated cases of acute angle-closure glaucoma without definite causal association have been reported with hydrochlorothiazide. Symptoms include acute onset of decreased visual acuity or ocular pain

and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug intake as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy (see Section 4.8 Adverse effects (undesirable effects)).

Photosensitivity

Photosensitivity reactions have been reported with the use of thiazide diuretics.

If the photosensitivity reactions occur during treatment with hydrochlorothiazide drugs, treatment should be stopped.

Heart Failure

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.

Cardiac Arrhythmia

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

Use in Hepatic Impairment

Karvezide should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations in fluid and electrolyte balance may precipitate hepatic coma.

Use in Renal Impairment

See comments under Renal Impairment, above.

Use in the Elderly

Among patients who received Karvezide 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

In premarketing controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of Karvezide tablets.

Creatinine, Blood Urea Nitrogen

Minor increases in blood urea nitrogen (BUN) or serum creatinine were observed in 2.3 and 1.1 percent, respectively, of patients with essential hypertension treated with Karvezide alone. No patient discontinued taking Karvezide due to increased BUN. One patient discontinued taking Karvezide due to a minor increase in creatinine.

Haemoglobin

Mean decreases of approximately 0.2 g/dL occurred in patients treated with Karvezide alone, but were rarely of clinical importance. This compared to a mean of 0.4 g/dL in patients receiving placebo. No patients were discontinued due to anaemia.

Liver Function Tests

Occasional elevations of liver enzymes and/or serum bilirubin have occurred. In patients with essential hypertension treated with Karvezide alone, one patient was discontinued due to elevated liver enzymes.

Serum Electrolytes

In double-blind clinical trials of various doses of irbesartan and hydrochlorothiazide, the incidence of hypertensive patients who developed hypokalaemia (serum potassium <3.5 mmol/L) was 7.5% versus 6.0% for placebo; the incidence of hyperkalaemia (serum potassium >5.7mmol/L) was <1.0% versus 1.7% for placebo. No patient discontinued due to increases or decreases in serum potassium. Overall, the combination of irbesartan and hydrochlorothiazide had no effect on serum potassium. Higher doses of irbesartan ameliorated the hypokalaemic response to hydrochlorothiazide (See Section 4.4 Special warnings and precautions for use).

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Based on *in vitro* data, no interactions with irbesartan would be expected to occur with drugs whose metabolism is dependent upon cytochrome P450 isoenzymes *CYP*1A1, *CYP*1A2, *CYP*2A6, *CYP*2B6, *CYP*2D6, *CYP*2E1 or *CYP*3A4. Irbesartan is primarily metabolized by *CYP*2C9, however, during clinical interaction studies, no significant pharmacokinetic and pharmacodynamic interactions were observed when irbesartan was co-administered with warfarin (a drug metabolized by *CYP*2C9).

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

Based on experience with the use of other drugs 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 potassium (eg trimethoprim containing medicines) with irbesartan may lead to increases in serum potassium, sometimes severe, and requires close monitoring of serum potassium. Concurrent therapy with hydrochlorothiazide may reduce the frequency of this effect.

Alcohol, barbiturates or narcotics

Potentiation of thiazide diuretic-induced orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin)

Thiazides may elevate blood glucose levels thus dosage adjustments of antidiabetic agents may be necessary.

Antigout medication

Dosage adjustments of antigout medication may be needed since hydrochlorothiazide may raise the blood level of uric acid.

Cardiac glycosides (e.g., digoxin) and other antiarrhythmic drugs (e.g., sotalol)

Diuretic-induced hypokalaemia may accentuate cardiac arrhythmias.

Calcium salts

Thiazide diuretics may increase serum calcium levels due to decreased excretion. If calcium or a calcium sparing drug (e.g. Vitamin D therapy) is prescribed, serum calcium levels should be monitored and calcium dosage adjusted accordingly.

Colestyramine resin and colestipol HCl

May delay or decrease absorption of hydrochlorothiazide. Karvezide should be taken at least one hour before, or four hours after these medications.

Lithium

Diuretic agents reduce the renal clearance of lithium and increase the risk of lithium toxicity. Increases in serum lithium concentrations and lithium toxicity have been reported with concomitant use of irbesartan. Co-administration with Karvezide should be approached with caution and frequent monitoring of serum lithium levels is recommended.

Inhibitors of Endogenous Prostaglandin Synthesis (i.e., NSAIDs)

In some patients, these agents can reduce the effects of thiazide diuretics.

Other diuretics and antihypertensive medications

The thiazide component of Karvezide may potentiate the actions of other antihypertensive drugs, especially ganglionic or peripheral adrenergic-blocking drugs. Hydrochlorothiazide may interact with diazoxide; blood glucose, serum uric acid levels and blood pressure should be monitored.

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.

The use of Karvezide in combination with an ACE inhibitor is contraindicated in patients with diabetic nephropathy (See Section 4.3 Contraindications and Section 4.5 Interactions with other medicines and other forms of interactions).

Renin inhibitor

The combination of Karvezide 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).

Angiotensin-Converting Enzyme inhibitors (ACE inhibitors)

The use of Karvezide in combination with an ACE inhibitor is contraindicated in patients with diabetic nephropathy and is not recommended in other patients.

Repaglinide

Irbesartan has the potential to inhibit OATP1B1. In a clinical study, it was reported that irbesartan increased the Cmax and AUC of repaglinide (substrate of OATP1B1) by 1.8-fold and 1.3-fold, respectively, when administered 1 hour before repaglinide. In another study, no relevant pharmacokinetic interaction was reported when the two drugs were co-administered. Therefore, dose adjustment of antidiabetic treatment such as repaglinide may be required (see 4.4 Special warnings and precautions for use).

Drugs used during surgery

The effects of nondepolarising muscle relaxants (e.g. tubocurarine), preanaesthetics and anaesthetics used in surgery may be potentiated by hydrochlorothiazide; dosage adjustments may be required. Preanaesthetic and anaesthetic agents should be given in reduced dosage, and if possible, hydrochlorothiazide therapy discontinued one week prior to surgery.

Carbamazepine

Concomitant use of carbamazepine and hydrochlorothiazide has been associated with the risk of symptomatic hyponatraemia. Electrolytes should be monitored during concomitant use. If possible, another class of diuretics should be used.

Pressor amines (eg noradrenaline)

Due to the thiazide component there is a possible decreased response to pressor amines but not sufficient to preclude their use.

Corticosteroids, ACTH

Intensified electrolyte depletion, particularly hypokalemia can occur with thiazide use.

Other interactions

The hypoglycaemic effect of beta-blockers and diazoxide may be enhanced by thiazides. Anticholinergic agents (e.g. atropine) may increase the bioavailability of thiazide-type diuretics by decreasing gastrointestinal motility and stomach emptying rate. Thiazides may increase the risk of adverse effects caused by amantadine. Thiazides may reduce the renal excretion of cytotoxic drugs (e.g. cyclophosphamide monohydrate, methotrexate) and potentiate their myelosuppressive effects.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

The effects of hydrochlorothiazide and the irbesartan/hydrochlorothiazide combination on fertility have not been evaluated in animal studies. However, with irbesartan alone, fertility and reproductive performance were not affected in studies of male and female rats at oral doses 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, Karvezide 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 Karvezide 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.

Thiazides cross the placental barrier and appear in cord blood. The routine use of diuretics in otherwise healthy pregnant women is not recommended and exposes mother and foetus to unnecessary hazard, including foetal or neonatal jaundice, thrombocytopenia and possibly other adverse reactions which have occurred in the adult.

No teratogenic effects were seen in rats given irbesartan and hydrochlorothiazide in combination at doses as high as 150/150 mg/kg/day. When pregnant rats were treated with irbesartan alone from day 0 to day 20 of gestation, at doses of 50 mg/kg/day and higher, transient effects (increased renal pelvic cavitation, hydroureter or subcutaneous oedema) were noted in full term rat foetuses but not in young animals necropsied after six 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 the 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. Hydrochlorothiazide is excreted in human breast milk. Thiazides in high doses causing intense diuresis can inhibit milk production. The use of Karvezide during breastfeeding is not recommended.

Because of the potential risk to the infant, a decision should be made whether to discontinue breastfeeding or to discontinue the drug, taking into account the importance of Karvezide to the therapy of the mother.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of Karvezide on the ability to drive motor vehicles or operate machinery have not been specifically studied, but based on its pharmacodynamic properties, Karvezide is unlikely to affect this ability. When driving vehicles or operating machinery, it should be taken into account that occasionally dizziness may occur during treatment of hypertension.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The combination of irbesartan and hydrochlorothiazide has been evaluated for safety in approximately 2750 subjects in clinical studies, including 1540 hypertensive patients treated for over 6 months and over 960 patients treated for one year or more. Adverse events in patients receiving Karvezide were generally mild and transient with no relationship to dose. The incidence of adverse events was not related to age, gender, or race.

In placebo-controlled clinical studies, including 898 irbesartan/hydrochlorothiazide-treated patients (usual duration of treatment 2 to 3 months), discontinuations due to any clinical or laboratory adverse event were 3.6 percent for irbesartan/hydrochlorothiazide-treated patients and 6.8 percent for placebo-treated patients (p=0.023).

Adverse events occurring in at least 1% of patients treated with irbesartan/hydrochlorothiazide, in placebo controlled trials are shown in Table 1 below.

The incidences of the same adverse events in the placebo, irbesartan and hydrochlorothiazide control groups are also shown.

Table 1 - Adverse Events in Placebo-Controlled Hypertension Trials

	Incidence Percentage (%) of Patients			
BODY SYSTEM/EVENT	Irbesartan/HCTZ n=898	Irbesartan n=400	HCTZ n=380	Placebo n=236
General				
Chest pain	1.8	1.5	1.6	1.3
Fatigue	6.5 *	4.0	3.2	3.0
Influenza	2.8	2.0	1.8	1.3
Cardiovascular				
Oedema	3.1	1.5	1.6	2.5
Tachycardia	1.2	0.5	0.5	0.4
Dermatology				
Rash	1.2	1.8	3.2	1.7
Gastrointestinal				
Abdominal pain	1.7	1.5	1.6	0.8
Anorectal disorder	1.0	0.3	0	0.4
Diarrhoea	2.1	2.8	1.1	3.4
Dyspepsia/heartburn	2.1	0.3	1.6	0.8
Nausea/vomiting	3.2 *	1.5	2.4	0.4
Immunology/Sensitivity disorder				
Allergy	1.1	0.5	0.5	0
Musculoskeletal/Connective Tissue				
Musc/skeletal pain	6.5	6.0	9.7*	4.7
Muscle cramp	1.0	0.8	2.1	1.3
Musculoskeletal trauma	1.3	2.0	1.8	0.8
Nervous System				
Anxiety/nervousness	1.0	1.0	0.5	1.7
Dizziness	7.6	5.5	4.7	4.2
Dizziness orthostatic	1.1	1.0	0.8	0.4
Headache	11.0 *	9.3 *	11.6	16.1
Renal/Genitourinary				
Abnormal urination	1.9	0.5	2.1	0.8
UTI	1.6	1.5	2.4	2.5

	Incidence Percentage (%) of Patients			
Respiratory				
Cough	2.2	2.3	2.6	3.0
Pharyngitis	2.1	2.3	2.9	1.7
Rhinitis	1.9	2.0	1.6	2.5
Sinus abnormality	2.9	4.5	3.2	4.7
Upper respiratory infection	5.6	8.3	7.1	5.5

* Statistically significant difference compared with placebo, p<0.05

Adverse reactions (clinical events probably or possibly related to therapy as determined by the clinical investigator) that occurred in more than 2 hypertensive patients when they were taking irbesartan/hydrochlorothiazide and no additional study medications in premarketing clinical trials involving 2700 subjects, and that were not reported in the above tabulation of adverse events, are listed in the following section.

These adverse reactions have been classified using standard terminology and are categorized by body system. They are listed in order of decreasing frequency according to the following definitions:

common: those adverse reactions occurring on one or more occasions in at least 1/100 but less than 1/10 patients;

uncommon: adverse reactions occurring in at least 1/1000 but less than 1/100 patients;

rare: those adverse reactions occurring in less than 1/1000 patients.

Cardiovascular

Uncommon - bradycardia; disturbance of cardiac rhythm; subjective disturbance of cardiac rhythm; disturbance of ventricular rhythm; ECG abnormality; flushing; hypotension; orthostatic hypotension; syncope.

Dermatologic

Uncommon - pruritus; skin discomfort.

Endocrine/Metabolic

Common - sexual dysfunction;

Uncommon - diabetes; gout; hot flashes; libido changes.

Gastrointestinal

Uncommon - constipation; decreased appetite; abdominal distention; dry mouth; epigastric pain; flatulence; gastroesophageal reflux.

General

Uncommon - cold sensation; hyperhidrosis; malaise; weakness; weight gain.

Musculoskeletal/Connective Tissue

Uncommon - abnormal reflexes; muscle ache; myalgia; extremity swelling; extremity weakness.

Common - significant increase in blood creatinine phosphokinase.

Nervous System

Uncommon - coordination disturbance; depression; emotional lability/disturbance; numbness; paraesthesia; sleep disturbance; somnolence; vertigo.

Respiratory

Uncommon - dry nasopharynx; dyspnoea; wheezing.

Special Senses

Uncommon - abnormal hearing; taste disturbance; vision disturbance.

Other clinical adverse reactions reported with the use of irbesartan or hydrochlorothiazide alone include:

Cardiovascular

Subjective rhythm disturbance, flushing, ECG abnormality, cardiac murmur, cardiac rhythm disturbance, orthostatic hypotension, atrial rhythm disturbance, conduction disorder, myocardial infarction.

Dermatologic

Facial erythema, dermatitis, acne, scalp-hair abnormality.

Endocrine/Metabolic/Electrolyte Imbalance

Breast disorder, hyperglycaemia, glycosuria, hyperuricaemia, electrolyte imbalance (including hyponatraemia and hypokalaemia).

Gastrointestinal

Abnormal stool, increased appetite, oral lesion, dysphagia, oesophagitis, anorexia, gastric irritation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialadenitis, xanthopsia.

General

Weakness, weight gain, warmth sensation, pain.

Haematopoietic

Leucopenia, neutropenia/agranulocytosis, thrombocytopenia, anaemia, aplastic anaemia, haemolytic anaemia.

Immunology/Sensitivity Disorder

Upper extremity oedema, head/neck oedema, photosensitivity reactions, fever, urticaria, necrotizing angiitis, (vasculitis, cutaneous vasculitis), respiratory distress (including pneumonitis and pulmonary oedema), anaphylactic reactions, toxic epidermal necrolysis.

Musculoskeletal/Connective Tissue

Arthritis, stiffness lower extremity, muscle spasm, weakness.

Nervous System

Stress related disorder, tremor, disturbing dreams, restlessness.

Renal/Genitourinary

Urination abnormality, renal dysfunction, interstitial nephritis.

Respiratory

Epistaxis.

Special Senses

Eye disturbance-other, eyelid abnormality, visual field abnormality, medication bad taste, eye disorders (transient blurred vision, secondary acute angle-closure glaucoma and/or acute myopia (see Section 4.4 Special warnings and precautions for use).

Postmarketing Experience

As with other angiotensin-II receptor antagonists, hypersensitivity reactions (urticaria, angioedema, anaphylactic reactions including anaphylactic shock) have been reported. The following have been reported during post marketing surveillance: vertigo, arthralgia, asthenia, hyperkalaemia, anaemia, thrombocytopenia (including thrombocytopenic purpura), myalgia, tinnitus, jaundice, elevated liver function tests, hepatitis, psoriasis (and psoriasis exacerbation) (see Section 4.4 Special warnings and precautions for use), photosensitivity, choroidal effusion, impaired renal function including cases of renal failure in patients at risk, and hypoglycaemia (see Section 4.4 Special warnings and precautions for use).

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

Frequency ‘not known’: Non-melanoma skin cancer* (Basal cell carcinoma and squamous cell carcinoma).

*Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed (see

Section 4.4 Special warnings and precautions for use and Section 5.1 Pharmacodynamic properties – clinical trials).

Acute respiratory distress syndrome (ARDS) (see Section 4.4 Special warnings and precautions for use).

Reporting suspected adverse effects

Reporting of 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 irbesartan doses of up to 900 mg/day for 8 weeks revealed no toxicity. No specific information is available on the treatment of overdosage with Karvezide. The patient should be closely monitored, and the treatment should be symptomatic and supportive, including fluid and electrolyte replacement. Irbesartan is not removed from the body by haemodialysis.

The most common signs and symptoms observed in adults exposed to hydrochlorothiazide are those caused by electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration resulting from excessive diuresis. If a cardiac glycoside (e.g. digoxin) or other antiarrhythmic drugs (e.g. sotalol) has also been administered, hypokalaemia may accentuate cardiac arrhythmias. The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: angiotensin II antagonists and diuretics, ATC code: C09DA04.

Mechanism of Action

Karvezide (irbesartan/hydrochlorothiazide) is an oral antihypertensive agent combining a nonpeptide angiotensin II receptor (AT_1 subtype) antagonist, irbesartan, and a thiazide diuretic, hydrochlorothiazide.

Irbesartan is a specific antagonist of angiotensin II receptors (AT_1 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 (AT_1 subtype) receptors localized on vascular

smooth muscle cells and in the adrenal cortex. It has no agonist activity at the AT_1 receptor and a much greater affinity (more than 8500-fold) for the AT_1 receptor than for the AT_2 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.

Hydrochlorothiazide is a benzothiadiazine (thiazide) diuretic with diuretic, natriuretic and antihypertensive effects. The mechanism of antihypertensive effect of thiazide diuretics, such as hydrochlorothiazide is not fully known. Thiazides affect the renal tubular mechanism of electrolyte reabsorption, increasing excretion of sodium and chloride in approximately equivalent amounts. Natriuresis causes a secondary loss of potassium and bicarbonate. Hydrochlorothiazide increases plasma renin activity, increases aldosterone secretion, and decreases serum potassium. Coadministration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with thiazide diuretics.

Clinical Trials

Based on data from placebo-controlled clinical trials, the following effects were noted. The blood pressure lowering effect of irbesartan in combination with hydrochlorothiazide was apparent after the first dose and substantially present within 1-2 weeks, with the maximal effect occurring by 6-8 weeks. In long-term follow-up studies, the blood pressure lowering effect of irbesartan/hydrochlorothiazide with dose-to-response addition of adjunctive therapy was maintained for over one year.

The combination of hydrochlorothiazide and irbesartan produced dose-related additive reductions in blood pressure across their therapeutic dose ranges. The addition of 12.5 mg hydrochlorothiazide to 300 mg irbesartan once daily in patients not adequately controlled on 300 mg irbesartan alone resulted in further placebo-corrected diastolic blood pressure reductions at trough (24 hours post dosing) of 6.1 mmHg. The combination of 300 mg irbesartan and12.5 mg hydrochlorothiazide resulted in an overall placebo-subtracted systolic/diastolic reduction of up to 13.6/11.5 mmHg.

Limited clinical data (7 out of 22 patients) suggest that patients not controlled with 300/12.5 mg combination may respond when uptitrated to 300/25 mg. In these patients, an incremental blood pressure lowering effect was observed for both SBP and DBP (13.3 and 8.3 mmHg, respectively).

Once daily dosing with 150 mg irbesartan and 12.5 mg hydrochlorothiazide showed systolic/diastolic mean placebo-adjusted blood pressure reductions at trough (24 hours post-dosing) of 12.9/6.9 mmHg. Peak effects occurred at 3-6 hours.

When assessed by ambulatory blood pressure monitoring, Irbesartan HCT Sanofi 150/12.5 once daily produced consistent reduction in blood pressure over the 24 hours period with a mean 24-hour placebo-subtracted systolic/diastolic reductions of 15.8/10.0 mmHg. The observed trough-to-peak effects were at least 68% of the corresponding placebo-subtracted peak diastolic and peak systolic responses.

In a clinical trial with patients not adequately controlled on 25 mg hydrochlorothiazide alone after 4 weeks' treatment, the addition of irbesartan (with dose-to-response uptitration from 75

mg to 150 mg at 6 weeks) produced mean systolic/diastolic reductions at 12 weeks which were 11.1/7.2 mmHg greater than hydrochlorothiazide alone.

Blood pressure was lowered to about the same extent in both standing and supine positions. Orthostatic effects were infrequent, but may be expected to occur in patients who develop intercurrent sodium and/or volume-depletion.

The effect of the combination of irbesartan and hydrochlorothiazide on morbidity and mortality has not been studied. Epidemiological studies have shown that long term treatment with hydrochlorothiazide reduces the risk of cardiovascular mortality and morbidity.

The effectiveness of irbesartan/hydrochlorothiazide was not influenced by age, race, or gender. The overall antihypertensive response to the combination was similar for black and non black patients.

After withdrawal of irbesartan, blood pressure gradually returned toward baseline. Rebound hypertension was not observed with irbesartan or hydrochlorothiazide.

With hydrochlorothiazide, onset of diuresis occurred in 2 hours, and peak effect occurred at about 4 hours, while the action persisted for approximately 6-12 hours.

Non-melanoma skin cancer:

Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and non-melanoma skin cancer has been observed. One study included a population comprised of 71, 553 cases of BCC and of 8,629 cases of SCC matched to 1,430,883 and 172,462 population controls, respectively. High HCTZ use (≥50,000 mg cumulative) was associated with an adjusted OR of 1.29 (95% CI: 1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for SCC. A clear cumulative dose-response relationship was observed for both BCC and SCC. Another study showed a possible association between risk of lip cancer (SCC) and exposure to HCTZ: 633 cases of lip cancer were matched with 63,067 population controls, using a risk-set sampling strategy. A clear cumulative dose-response relationship was demonstrated with an adjusted OR 2.1 (95% CI: 1.7-2.6) for ever-use, OR 3.9 (3.0-4.9) for high use (at least 25,000 mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose (at least 100,000 mg) (see Section 4.4 Special warnings and precautions for use).

5.2 PHARMACOKINETIC PROPERTIES

Concomitant administration of hydrochlorothiazide and irbesartan has no effect on the pharmacokinetics of either drug

Absorption

The oral bioavailabilities of irbesartan and hydrochlorothiazide measured after administration of Karvezide are similar to the bioavailabilities of irbesartan and hydrochlorothiazide administered as separate entities. The absolute oral bioavailability for irbesartan has previously been shown to be 60-80% whilst the absolute oral bioavailability for hydrochlorothiazide is documented as 50-80%.

Food does not affect the bioavailability of Karvezide. Peak plasma concentrations occur 1.5-2 hours after oral administration for irbesartan and 1-2.5 hours for hydrochlorothiazide.

Distribution

Irbesartan is 90% protein-bound in the plasma, and has negligible binding to cellular components of blood. The volume of distribution is 53-93 litres (0.72-1.24 L/kg). Hydrochlorothiazide is 68% protein-bound in the plasma, and its apparent volume of distribution is 0.83-1.141 L/kg.

Metabolism

In plasma, unchanged irbesartan accounts for more than 80% of the circulating radioactivity following oral or intravenous administration of ^{14}C irbesartan. Irbesartan is metabolized 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 *CYP*2C9; isoenzyme *CYP*3A4 has negligible effect. It is not metabolized by, nor does it substantially induce or inhibit most isoenzymes commonly associated with drug metabolism (i.e., *CYP*1A1, *CYP*1A2, *CYP*2A6, *CYP*2B6, *CYP*2D6, or *CYP*2E1). Irbesartan does not induce nor inhibit isoenzyme *CYP*3A4.

Hydrochlorothiazide is not metabolized.

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 ^{14}C irbesartan is recovered in urine with the remainder in the faeces. Less than 2% of the dose is excreted in urine as unchanged irbesartan.

The terminal elimination half-life (t½) of irbesartan from plasma is 11-15 hours. The total body clearance of intravenously administered irbesartan is 157-176 mL/min, of which 3.0-3.5mL/min is 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.

Hydrochlorothiazide is eliminated by the kidneys. The mean plasma half-life (t½) of hydrochlorothiazide from plasma reportedly ranges from 5-15 hours.

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 concentration (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. The area under the plasma concentration time curve (AUC) for hydrochlorothiazide was elevated in the elderly group following multiple dosing consistent with previously published data.

In black and white normotensive subjects, the plasma AUC and t½ 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 severe renal impairment (creatinine clearance <20 mL/min), the elimination half-life of hydrochlorothiazide was reported to increase to 21 hours.

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 and the irbesartan/hydrochlorothiazide combination were not genotoxic in a series of assays for gene-mutagenic activity in bacterial and mammalian cells, and for clastogenic effects *in vitro* and *in vivo*. Hydrochlorothiazide alone was not genotoxic in a gene-mutation assay in bacterial cells, or in tests for clastogenic activity *in vitro* and *in vivo*. However, positive results were obtained in a mammalian cell assay for gene mutation (mouse lymphoma cell assay) and in two other tests (sister chromatid exchange assay in Chinese hamster ovary cells and non-disjunction assay in *Aspergillus nidulans*).

Carcinogenicity

The carcinogenic potential of irbesartan and hydrochlorothiazide in combination has not been evaluated in animal studies. However, 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. With hydrochlorothiazide two year feeding studies in mice and rats uncovered no evidence of carcinogenic potential in female mice at doses up to approximately 600 mg/kg/day, or in male and female rats at doses up to approximately 100 mg/kg/day. The studies, however, uncovered equivocal evidence for hepatocarcinogenicity in male mice treated with hydrochlorothiazide at approximately 600 mg/kg/day.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The inactive ingredients in Karvezide 150/12.5 & 300/12.5 tablets include: carnauba wax, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, OPADRY II complete film coating system 32F24503 PINK, and silicon dioxide.

The inactive ingredients in Karvezide 300/25 tablets include: carnauba wax, croscarmellose sodium, iron oxide red, iron oxide yellow, lactose monohydrate, magnesium stearate,

microcrystalline cellulose, pregelatinised maize starch, OPADRY II Complete film coating system 32F24304 PINK, and silicon dioxide.

6.2 INCOMPATIBILITIES

Incompatibilities were either not accessed 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

Pack sizes include: 3*, 5*, 7§, 14*, 28*, 30, 56* and 98* tablets in polyvinyl chloride/polyvinylidene chloride/aluminium (PVC/PVDC/Al) blisters.

* presentations currently not-marketed

§ starter pack

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 PHYSICOCHEMICAL PROPERTIES

Irbesartan: 2-butyl-3-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-1,3-diazaspiro [4,4] non-1-en-4-one.

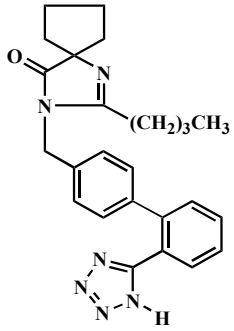
Irbesartan is a white to off-white crystalline powder. It is a relatively non-polar compound with a partition coefficient (octanol-water) of 10.1 at a pH of 7.4. Irbesartan is slightly soluble in alcohol and methylene chloride, and practically insoluble in water.

Hydrochlorothiazide: 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

Hydrochlorothiazide is a white crystalline powder. It is slightly soluble in water but freely soluble in sodium hydroxide solution.

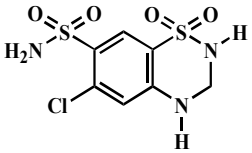
Chemical Structure

The chemical structure of irbesartan is



The empiric formula is $C_{25}H_{28}N_6O$ and the molecular weight, 428.5.

The chemical structure of hydrochlorothiazide is:



The empiric formula is $C_7H_8ClN_3O_4S_2$ and the molecular weight, 297.7.

CAS Number

Irbesartan CAS number: 138402-11-6

Hydrochlorothiazide CAS number: 58-93-5

7 MEDICINE SCHEDULE

Schedule 4

8 SPONSOR

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9 DATE OF FIRST APPROVAL

18 May 2005

10 DATE OF REVISION

22 August 2022

Karvezide is a sanofi-aventis trademark.

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	Addition of acute respiratory toxicity
4.8	Addition of blood creatinine phosphokinase increase and ARDS