PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

IRBECARD 75 mg, 150 mg and 300 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

IRBECARD 75 mg: Each film-coated tablet contains 75 mg irbesartan.

IRBECARD 150 mg: Each film-coated tablet contains 150 mg irbesartan.

IRBECARD 300 mg: Each film-coated tablet contains 300 mg irbesartan.

Excipient with known effect:

IRBECARD 75 mg: 13,0 mg of lactose monohydrate per film-coated tablet

IRBECARD 150 mg: 26,0 mg of lactose monohydrate per film-coated tablet

IRBECARD 300 mg: 52,0 mg of lactose monohydrate per film-coated tablet

For full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

IRBECARD 75 mg: A white to off-white, oblong, biconvex, film-coated tablet.

IRBECARD 150 mg: A white to off-white, oblong, biconvex film-coated tablet with score line and ‘G’ embossed on one side and plain on the other side.

IRBECARD 300 mg: A white to off-white, oblong, biconvex film-coated tablet with score line.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

IRBECARD is indicated for the treatment of essential hypertension. It may be used either alone or in combination with other antihypertensive medicines. IRBECARD is indicated for the treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria (> 300 mg/day) in patients with type 2 diabetes and hypertension.

4.2 Posology and method of administration

Posology

The usual recommended initial and maintenance dose is 150 mg once daily, with or without food.

In patients insufficiently controlled with 150 mg once daily, the dose of IRBECARD may be increased to 300 mg, or other antihypertensive medicines may be added.

In patients with hypertension and type 2 diabetic renal disease, 300 mg of IRBECARD once daily is the preferred maintenance dose.

Special populations

Elderly patients and patients with renal or hepatic impairment

No dosage reduction is generally necessary in the elderly or in patients with impaired renal function or impaired hepatic function (mild to moderate degree).

Patients with intravascular volume depletion

See section 4.4: ***'Intravascular volume depletion'.***

Paediatric population

Safety and efficacy in paediatric patients have not been established.

Method of administration

For oral use.

4.3 Contraindications

IRBECARD is contraindicated in patients who have the following:

- hypersensitivity to irbesartan or to any of the ingredients of IRBECARD.
- a history of angioedema related to previous therapy with angiotensin receptor blockers (ARBs) or angiotensin converting enzyme inhibitors (ACEIs): these patients must never again be given these medicines.
- hereditary or idiopathic angioedema.
- hypertrophic obstructive cardiomyopathy (HOCM).
- severe renal function impairment (creatinine clearance less than 30 mL/min).
- moderate to severe renal impairment, and concomitantly using fluoroquinolones.
- bilateral renal artery stenosis.
- renal artery stenosis in patients with single kidney, or a transplanted kidney.
- aortic stenosis.
- concomitant therapy with potassium-sparing diuretics such as spironolactone, triamterene, amiloride.
- porphyria.
- lithium therapy: concomitant administration with IRBECARD may lead to toxic blood concentrations of lithium (see sections 4.4 and 4.5).
- pregnancy and lactation (see sections 4.4 and 4.6).
- the concomitant use of IRBECARD with aliskiren-containing products (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Should a woman become pregnant while receiving IRBECARD, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine (see sections 4.3 and 4.6).

Intravascular volume depletion

IRBECARD has been associated with hypotension in hypertensive patients without other co-morbid conditions. 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 IRBECARD or a lower starting dose (IRBECARD 75 mg) should be considered (See section 4.2).

Renal impairment and kidney transplantation

When IRBECARD is used in patients with impaired renal function, a periodic monitoring of potassium and creatinine serum levels is recommended (see section 4.5). As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. There is no experience regarding the administration of IRBECARD in patients with a recent kidney transplantation.

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 medicines that affect the renin-angiotensin-aldosterone system. While this is not documented with IRBECARD, a similar effect should be anticipated with angiotensin II receptor antagonists. The use of IRBECARD in patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney is contraindicated (see section 4.3).

Fluoroquinolones and ARBs

Concomitant use of fluoroquinolones and ARBs such as IRBECARD may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients (see section 4.3). Renal function should be assessed before initiating treatment and monitored during treatment with fluoroquinolones or ARBs such as IRBECARD whether used separately and/or concomitantly.

Lithium

The combination of lithium and IRBECARD is contraindicated (see sections 4.3 and 4.5).

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy

Special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy (see section 4.3).

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

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 or angiotensin II receptor blockers such as IRBECARD is therefore not recommended (see section 4.5). ACE-inhibitors and angiotensin II receptor blockeRs should not be used concomitantly in patients with diabetic nephropathy.

IRBECARD should not be used concomitantly with aliskiren (see section 4.3).

Hyperkalaemia

Hyperkalaemia may occur during the treatment with IRBECARD, 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 section 4.5).

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 IRBECARD 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, uraemia, oliguria, or acute renal failure (see section 4.5). Excessive blood pressure decreases in patients with ischaemic cardiopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke.

Lactose

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

4.5 Interactions with other medicines and other forms of interaction

Fluoroquinolones

Concomitant use of ARBs as in IRBECARD and fluoroquinolones may precipitate acute kidney injury. The mechanism of the possible interaction between the different classes of medicines, over and above different mechanisms of kidney damage, is unknown (see section 4.3).

Potassium supplements and potassium-sparing diuretics

Based on experience with the use of other medicines that affect the renin-angiotensin system, concomitant use of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicines that may increase serum potassium levels (e.g.

heparin) may lead to increases in serum potassium and is, therefore, not recommended (see section 4.4). The use of potassium-sparing diuretics with IRBECARD is contraindicated (see section 4.3).

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 reported with IRBECARD so far. Therefore, this combination is contraindicated (see section 4.3).

Non-steroidal anti-inflammatory drugs

When angiotensin II antagonists are administered simultaneously with nonsteroidal anti-inflammatory drugs (NSAIDs) (i.e. selective COX-2 inhibitors, acetylsalicylic acid (> 3 g/day) and non-selective NSAIDs), attenuation of the antihypertensive effect may occur.

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. These effects may be reversible. The combination should be administered with caution, especially in the elderly, volume-depleted (including those on diuretic therapy) or with compromised renal function.

Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

Diuretics and other antihypertensive medicines

Other antihypertensive medicines may increase the hypotensive effects of irbesartan; however IRBECARD has been safely administered with other antihypertensive medicines, 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 IRBECARD (see section 4.4).

Dual blockade of the RAAS with ARBs 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 medicine (see section 4.4).

Additional information on IRBECARD interactions

The pharmacokinetics of IRBECARD is not affected by nifedipine or hydrochlorothiazide.

IRBECARD is mainly metabolised by CYP2C9 and to a lesser extent by glucuronidation. No significantly pharmacokinetic or pharmacodynamic interactions are observed when IRBECARD is co-administered with warfarin, a medicine metabolised by CYP2C9.

The effects of CYP2C9 inducers such as rifampicin on the pharmacokinetics of IRBECARD have not been evaluated.

The pharmacokinetics of digoxin or simvastatin are not altered by co-administration of IRBECARD.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing age should ensure effective contraception.

Pregnancy

Safety in pregnancy has not been established (see sections 4.3 and 4.4). When pregnancy is planned or confirmed, IRBECARD should be discontinued.

Medicines affecting the renin-angiotensin system, such as IRBECARD, can cause embryonal toxicity, foetal and neonatal morbidity and mortality when administered in pregnant women. Patients planning pregnancy should be changed to alternative antihypertensive treatments, which have an established safety profile for use in pregnancy.

Breastfeeding

Safety in lactation has not been established. It is unknown whether irbesartan or its metabolites are excreted in human milk.

Available pharmacodynamics/toxicological data in rats have shown excretion of irbesartan or its metabolites in milk.

Fertility

IRBECARD had no effect upon fertility of treated rats and their offspring up to the dose levels inducing the first signs of parental toxicity.

4.7 Effects on ability to drive and use machines

IRBECARD may cause dizziness and fatigue which may affect the ability to drive and use machines. Caution is advised before driving or operating machinery until the effects of IRBECARD are known.

4.8 Undesirable effects

The following adverse reactions have been reported during clinical trials in patients with hypertension:

Nervous system disorders

Frequent: dizziness, headache

Cardiac disorders

Less frequent: tachycardia

Vascular disorders

Less frequent: flushing

Respiratory, thoracic and mediastinal disorders

Less frequent: cough

Gastrointestinal disorders

Frequent: nausea, vomiting

Less frequent: diarrhoea, dyspepsia/heartburn

Hepatobiliary disorders

Less frequent: jaundice

Reproductive system and breast disorders

Less frequent: sexual dysfunction

General disorders and administration site conditions

Frequent: fatigue

Less frequent: chest pain

Investigations

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 essential hypertension receiving therapy with IRBECARD.

Other

Frequency unknown: Oedema

The following adverse reactions have been reported during clinical trials in patients with hypertension and type 2 diabetic renal disease:

Nervous system disorders

Frequent: dizziness, orthostatic dizziness

Vascular disorders

Frequent: orthostatic hypotension

Musculoskeletal and connective tissue disorders

Frequent: musculoskeletal pain

Investigations

Frequent: hyperkalaemia, increased plasma creatine kinase[1], decrease in haemoglobin[2]

[1] None of these increases were associated with identifiable clinical musculoskeletal events.

[2] In hypertensive patients with advanced diabetic renal disease treated with irbesartan. The decrease in haemoglobin was not clinically significant.

The following adverse reactions have been reported during post-marketing experience:

Blood and lymphatic system disorders

Frequency unknown: thrombocytopenia

Immune system disorders

Frequency unknown: hypersensitivity reactions (such as angioedema, rash, urticaria, anaphylactic reaction, anaphylactic shock)

Metabolism and nutrition disorders

Frequency unknown: hyperkalaemia

Nervous system disorders

Frequency unknown: vertigo, headache

Ear and labyrinth disorders

Frequency unknown: tinnitus

Gastrointestinal disorders

Frequency unknown: dysguesia

Hepatobiliary disorders

Frequency unknown: abnormal liver function, jaundice, hepatitis

Skin and subcutaneous tissue disorders

Frequency unknown: leukocytoclastic vasculitis

Musculoskeletal and connective tissue disorders

Frequency unknown: arthralgia, myalgia (in some cases associated with increased plasma creatine kinase levels), muscle cramps

Renal and urinary disorders

Frequency unknown: Impaired renal function including cases of renal failure of patients at risk (see section 4.4)

General disorders and administration site conditions

Frequency unknown: asthenia

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions after authorisation of IRBECARD is important. It allows continued monitoring of the benefit/risk balance of IRBECARD. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 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 overdosage with IRBECARD. The patient should be closely monitored and the treatment should be symptomatic and supportive. Suggested measures include induction of emesis. Activated charcoal may be useful in the treatment of overdose. IRBECARD is not removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 7.1.3 Other hypotensives

Pharmacotherapeutic group: Angiotensin II antagonists, plain.

ATC code: C09C A04

Mechanism of action

Irbesartan is a specific antagonist of angiotensin II receptor (AT_1 subtype), known as an angiotensin receptor blocker (ARB). Angiotensin II is an important component of the renin-angiotensin system (RAS) and is involved in the pathophysiology of hypertension and sodium homeostasis.

Irbesartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selective antagonism of the angiotensin II (AT_1 subtype) receptors localised 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.

Irbesartan blockade of AT_1 receptors interrupts the feedback loop within the renin-angiotensin system, resulting in increases in plasma renin levels and angiotensin II levels.

Aldosterone plasma concentrations decline following irbesartan administration. However, serum potassium levels are not significantly affected (mean increase of < 0,1 mmol/L) at the recommended doses. Irbesartan has no notable effects on serum triglycerides, cholesterol or glucose concentrations. There is no effect on serum uric acid or urinary uric acid excretion.

5.2 Pharmacokinetic properties

Absorption

Irbesartan is orally active and does not require biotransformation for its activity. 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. Peak plasma concentration occurs at 1,5 - 2 hours after oral administration.

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 ^{14}C 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 %). Irbesartan undergoes oxidation primarily by the cytochrome P450 isoenzyme 2C9; isoenzyme 3A4 has negligible effect. It is not metabolised by, nor does it substantially induce or inhibit most isoenzymes commonly associated with metabolism of medicines (i.e. 1A1, 1A2, 2A6, 2B6, 2D6 or 2E1). Irbesartan does not induce or inhibit isoenzyme 3A4.

Elimination

Irbesartan and its metabolites are eliminated by both biliary and renal pathways. After either oral or intravenous administration of ^{14}C 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 urine as unchanged irbesartan.

Linearity/non-linearity

Irbesartan exhibits linear and dose proportional pharmacokinetics over the therapeutic dose range. Peak plasma concentrations are attained at 1,5 – 2 hours after oral administration.

The total body and renal clearance are 157 - 176 and 3,0-3,5 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.

Special populations

Race

In black and white normotensive subjects, the plasma AUC and $t_{½}$ of irbesartan are approximately 20 - 25 % greater in blacks than in whites; the peak plasma concentrations (C_{max}) of irbesartan are essentially equivalent.

Gender

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.

Elderly

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.

Renal impairment

In patients with renal impairment (regardless of degree) or those undergoing haemodialysis, the pharmacokinetic~~s~~ parameters of irbesartan are not significantly altered. Irbesartan is not removed by haemodialysis.

Hepatic impairment

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

5.3. Preclinical safety data

No further information of relevance available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core: Microcrystalline cellulose, pregelatinised starch, lactose monohydrate, poloxamer 188, croscarmellose sodium, magnesium stearate.

Film-coating: Hydroxypropyl cellulose, hypromellose 6cP, titanium dioxide, talc.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

3 years

6.4 Special precautions for storage

Store at or below 30 °C in the original package.

Do not remove the blisters from the carton until required for use.

6.5 Nature and contents of container

The film-coated tablets are packed in PVC/PVDC/Aluminium foil blisters strips. The blister strips are packed in cartons containing 28 or 30 tablets.

Not all pack sizes are marketed at any one time.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Smart Pharmaceuticals (Pty) Ltd

247 Voortrekker Road

Kraaifontein, Cape Town

7570

8. REGISTRATION NUMBERS

IRBECARD 75 mg: 47/7.1.3/0732

IRBECARD 150 mg: 47/7.1.3/0733

IRBECARD 300 mg: 47/7.1.3/0734

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28 February 2022

10. DATE OF REVISION OF THE TEXT

28 February 2022

IRB/C/PI/A