PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

CO-IRBECARD 150/12,5 mg tablets

CO-IRBECARD 300/12,5 mg tablets

CO-IRBECARD 300/25 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CO-IRBECARD 150/12,5 mg tablets contain 150 mg of irbesartan and 12,5 mg hydrochlorothiazide.

CO-IRBECARD 300/12,5 mg tablets contain 300 mg of irbesartan and 12,5 mg hydrochlorothiazide.

CO-IRBECARD 300/25 mg tablets contain 300 mg of irbesartan and 25 mg hydrochlorothiazide.

Contains sugar:

CO-IRBECARD 150/12,5 mg tablets – 26,0 mg lactose monohydrate per tablet.

CO-IRBECARD 300/12,5 mg tablet – 52,0 mg lactose monohydrate per tablet.

CO-IRBECARD 300/25 mg tablet – 52,0 mg lactose monohydrate per tablet.

For full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

CO-IRBECARD 150/12,5 mg: A light pink, oblong, biconvex film-coated tablet.

CO-IRBECARD 300/12,5 mg: A light pink, oblong, biconvex film-coated tablet.

CO-IRBECARD 300/25 mg: A red-brick, oblong, biconvex, film-coated tablet with a score line. The score line on Co-Irbecard 300/25 mg tablet is non-functional, instead it is just for discrimination with other strengths.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CO-IRBECARD is indicated for the treatment of essential hypertension in patients stabilised on the individual components at the same dosages.

CO-IRBECARD may also be used as initial therapy in previously untreated patients with sitting diastolic blood pressure of 100 mm Hg or higher, or in patients previously treated with one of the components of CO-IRBECARD whose diastolic blood pressure is 100 mm Hg or higher.

The choice of CO-IRBECARD as initial therapy for hypertension should be based on an assessment of potential benefits and risks.

4.2 Posology and method of administration

Posology

Essential hypertension in patients stabilised on the individual components at the same dosages

One tablet daily with or without food.

CO-IRBECARD is indicated for use in patients who are adequately controlled on the individual components at the same dosages.

If blood pressure is not adequately controlled with CO-IRBECARD alone. another antihypertensive medicine (e.g. beta-adrenergic blocking medicine, long-acting calcium channel blocking medicine) may be added.

Initial therapy

The usual starting dose is CO-IRBECARD 150/12,5 mg once daily. The dosage can be increased after 1 to 2 weeks of therapy to 300/12,5 mg once daily as needed to control blood pressure.

CO-IRBECARD 300 mg/25 mg may be administered in patients insufficiently controlled by CO-IRBECARD 300 mg/12,5 mg.

Doses higher than 300 mg irbesartan/25 mg hydrochlorothiazide once daily are not recommended.

Special populations

Elderly patients and patients with renal or hepatic impairment

No dosage reduction is generally necessary in the elderly or in patients with mild to moderate renal impairment (creatinine clearance > 30 ml/min).

However, due to the hydrochlorothiazide component, CO-IRBECARD is not recommended for patients with severe renal dysfunction (creatinine clearance < 30 ml/min (see section 4.4).

No dosage reduction is generally necessary in patients with mild to moderate hepatic impairment. Due to the hydrochlorothiazide component. CO-IRBECARD should be used with caution in patients with severe hepatic impairment (see section 4.4).

Patients with intravascular volume depletion

Volume and/or sodium depletion should be corrected prior to administration of CO-IRBECARD (see section 4.4)

Paediatric population:

CO-IRBECARD is not recommended for use in children and adolescents because the safety and efficacy have not been established.

Method of administration

CO-IRBECARD is for oral administration with a glass of water.

4.3 Contraindications

CO-IRBECARD is contraindicated in patients with:

- hypersensitivity to irbesartan, sulphonamide derived medicines (e.g. thiazides) or to any other component of the CO-IRBECARD formulation (see section 6.1). In general. hypersensitivity reactions are more likely to occur in patients with a history of allergy or bronchial asthma
- a history of angioedema related to previous therapy with ACE inhibitors or ARBs. 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 (see section 4.5)
- porphyria - hydrochlorothiazide has been associated with acute attacks of porphyria
- thiazide diuretics in (fixed dose) combination with irbesartan [i. e. CO-IRBECARD) should not be given to patients with Addison's disease. This therapy is also contraindicated in patients with severe renal impairment or anuria
- lithium therapy: Concomitant administration with CO-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)
- concomitant use of CO-IRBECARD with direct renin inhibitors such as aliskiren-containing medicines (see sections 4.4. and 4.5)

***Paediatric use*:** Safety and efficacy in paediatric patients have not been established.

4.4 Special warnings and precautions for use

Pregnancy and lactation:

Should a woman become pregnant while receiving CO-IRBECARD, the treatment should be stopped immediately and the patient switched to a different class of medicine of which the main action does not directly affect the RAAS (see sections 4.3 and 4.6).

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.

Hypotension – Volume-depleted patients: CO-IRBECARD has been associated with hypotension in hypertensive patients without other risk factors for hypotension. Symptomatic hypotension 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 CO-IRBECARD. Thiazides may potentiate the action of other antihypertension medicines (see section 4.5).

Renal artery stenosis - 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 angiotensin converting enzyme inhibitors or angiotensin-II receptor antagonists. While this is not documented with CO-IRBECARD, a similar effect should be anticipated.

Renal impairment and kidney transplantation: when CO-IRBECARD is used in patients with impaired renal function, a periodic monitoring of potassium, creatinine and uric acid serum levels is recommended. There is no experience regarding the administration of CO-IRBECARD in patients with a recent kidney transplantation. CO-IRBECARD should not be

used in patients with severe renal impairment (creatinine clearance < 30 ml/min) (see section 4.3). Thiazide diuretic-associated azotaemia may occur in patients with impaired renal function. No dosage adjustment is necessary in patients with renal impairment whose creatinine clearance is ≥ 30 ml/min. However, in patients with mild to moderate renal impairment (creatinine clearance ≥ 30 ml/min but < 60 ml/min) this fixed dose combination should be administered with caution.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS) There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers (ARBs) or aliskiren may increase the risk of hypotension, hyperkalaemia and decreases renal function (including acute renal failure). Dual blockade of RAAS through the combined use of CO-IRBECARD and aliskiren is therefore contraindicated (see section 4.3).

Hepatic impairment: thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. There is no clinical experience with CO-IRBECARD in patients with hepatic impairment.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy: as with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Primary aldosteronism: patients with primary aldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of CO-IRBECARD is not recommended.

Metabolic and endocrine effects: thiazide therapy may impair glucose tolerance. In diabetic patients dosage adjustments of insulin or oral hypoglycaemic medicines may be required. Latent diabetes mellitus may become manifest during thiazide therapy.

Increases in cholesterol and triglyceride levels have been associated with thiazide diuretic therapy; however at the 12,5 mg dose contained in CO-IRBECARD, minimal or no effects were reported.

Hyperuricaemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

Electrolyte imbalance: as for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals.

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

Although hypokalaemia may develop with the use of thiazide diuretics, concurrent therapy with irbesartan may reduce diuretic-induced hypokalaemia. The risk of hypokalaemia is greatest in patients with cirrhosis of the liver, in patients experiencing brisk diuresis, in patients who are receiving inadequate oral intake of electrolytes and in patients receiving concomitant therapy with corticosteroids or ACTH. Conversely, due to the irbesartan component of CO-IRBECARD hyperkalaemia might occur, especially in the presence of renal impairment and/or heart failure, and diabetes mellitus. Adequate monitoring of serum potassium in patients at risk is recommended. Potassium-sparing diuretics, potassium supplements or potassium-containing salts substitutes should be co-administered cautiously with CO-IRBECARD (see section 4.5).

There is no evidence that irbesartan would reduce or prevent diuretic-induced hyponatraemia. Chloride deficit is generally mild and usually does not require treatment.

Thiazides may decrease urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism.

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 hypomagnaesemia.

Fluoroquinolones and ARBs:

Concomitant use of fluoroquinolones and ARBs 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 whether used separately and/or concomitantly.

Lithium:

The combination of lithium and CO-IRBECARD is contraindicated (refer to sections 4.3 and 4.5).

General:

In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with angiotensin converting enzyme inhibitors or angiotensin-II receptor antagonists that affect this system has been associated with acute hypotension, azotaemia, oliguria, or acute renal failure (see section 4.5). As with any antihypertensive medicine, excessive blood pressure decrease in patients with ischemic cardiopathy or ischemic cardiovascular disease could result in a myocardial infarction or stroke.

Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.

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

Cases of photosensitivity reactions have been reported with thiazides diuretics (see section 4.8). If photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If a re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Acute myopia and secondary acute angle-closure glaucoma: sulfonamide medicines or sulfonamide derivative medicines can cause an idiosyncratic reaction, resulting in transient myopia and acute angle-closure glaucoma. While hydrochlorothiazide is a sulfonamide, only isolated cases of acute angle-closure glaucoma have been reported so far with hydrochlorothiazide. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of medicine initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue medicine 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).

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.

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 UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize 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 NMSC (see also section 4.8).

Information about excipients

CO-IRBECARD contains lactose monohydrate (see section 6.1). Patients with rare hereditary problems of galactose intolerance, e.g. galactosaemia, the Lapp lactase deficiency or glucose-galactose malabsorption, should not take CO-IRBECARD.

4.5 Interactions with other medicines and other forms of interactions

Based on *in vitro* data, no interactions would be expected to occur with medicines whose metabolism is dependent on cytochrome P450 isoenzymes CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2D6, CYP2E1 or CYP3A4.

Irbesartan is primarily metabolised by CYP2C9, however, during clinical interaction studies, no significantly pharmacodynamics interactions were observed when irbesartan was co-administered with warfarin (a medicine metabolised by CYP2C9).

Irbesartan does not affect the pharmacokinetics of digoxin or simvastatin.

The pharmacokinetics of irbesartan is not affected by co-administration with nifedipine or hydrochlorothiazide.

Based on experience with the use of other medicines 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. Concurrent therapy with hvdrochlorothiazide may reduce the frequency of this effect.

Alcohol, barbiturates or narcotics·- Potentiation of thiazide diuretic-induced orthostatic hypotension may occur.

Antidiabetic medicines oral medicines and insulin - Thiazides may elevate blood glucose levels thus, dosage adjustments of antidiabetic medicines 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 anti-dysrhythmic medicines (e.g. sotalol) - Diuretic induced hypokalaemia may accentuate cardiac dysrhythmias.

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

Cholestyramine resin and colestipol hydrochloride·- May delay or decrease absorption of hydrochlorothiazide. CO-IRBECARD should be taken at least one hour before or four hours after these medications.

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

As with ACE inhibitors, concomitant use of angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

Inhibitors of endogenous prostaglandin synthesis (i.e. non-steroidal anti-inflammatory medicines) - In some patients these medicines can reduce the effects of thiazide diuretics.

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 irbesartan. Furthermore, renal clearance of lithium is reduced by thiazides so the risk of lithium toxicity could be increased with CO-IRBECARD. Therefore, the combination is contraindicated (see section 4.3).

Other diuretics and antihypertensive medications·- The thiazide component or CO-IRBECARD may potentiate the actions of other antihypertensive medicines, especially ganglionic or peripheral adrenergic-blocking medicines. Hydrochlorothyazide may interact with diazoxide; blood glucose, serum uric acid levels and blood pressure should be monitored.

Medicines used during surgery·- The effects of non-depolarising muscle relaxants, pre-anaesthetics and anaesthetics used in surgery (e.g. tubocurarine) may be potentiated by hydrochlorothiazide: dosage adjustments may be required. Pre-anaesthetic and anaesthetic medicines should be given in reduced dosage, and if possible,-hydrochlorothiazide therapy discontinued one week prior to surgery.

Concomitant use of ARBs 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).

Dual blockade of the RAAS with ARBs, ACE inhibitors, or aliskiren - 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 (see sections 4.3 and 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

CO-IRBECARD is contraindicated in pregnancy (see sections 4.3 and 4.4)

CO-IRBECARD can cause foetal morbidity and death. CO-IRBECARD passes through the placenta and can be presumed to cause disturbances in foetal blood pressure regulatory mechanisms. Oligohydramnios, as well as hypotension, oliguria and anuria in newborns have been reported after administration of ARBs such as CO-IRBECARD in the second and third trimesters of pregnancy. Cases of defective skull ossification have been observed. Prematurity and low birth mass can occur.

Women of Childbearing Potential

Women of childbearing age should ensure effective contraception.

Breastfeeding

CO-IRBECARD is contraindicated in lactation (see section 4.3).

Fertility

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

4.7 Effects on ability to drive and use machines

Based on its pharmacodynamic properties, CO-IRBECARD is unlikely to affect the ability to drive and use machines. 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 Undesirable effects

Adverse reactions have been ranked under the heading of system-organ class and frequency indicated as frequent, less frequent and isolated cases.

Irbesartan/hydrochlorothiazide combination:

Immune system disorders

Less frequent: rash

Nervous system disorders

Frequent: dizziness, headache

Less frequent: orthostatic hypotension

Cardiac disorders

Less frequent: hypotension, oedema, syncope, tachycardia

Vascular disorders

Less frequent: flushing

Gastrointestinal disorders

Frequent: nausea/vomiting

Less frequent: diarrhoea, dry mouth

Musculoskeletal, connective tissue and bone disorders

Less frequent: swelling of the extremities, muscle/skeletal pain

Renal and urinary disorders

Frequent: abnormal urination

Reproductive system and breast disorders

Less frequent: libido changes, sexual dysfunction

General disorders and administration site conditions

Frequent: fatigue

Less frequent: weakness

Adverse reactions reported from post-marketing experience:

Immune system disorders: cases of hypersensitivity reactions (angioedema, urticaria) have been reported.

Metabolism and nutrition disorders: hyperkalaemia

Respiratory, thoracic and mediastinal disorders: cough

Gastrointestinal disorders: dyspepsia

Hepatobiliary disorders: elevated liver function tests. jaundice, hepatitis

Musculoskeletal, connective tissue and bone disorders: myalgia

Renal and urinary disorders: impaired renal function including isolated cases of renal failure in patients at risk.

General disorders and administration site conditions: asthenia

Additional information on individual components: in addition to the adverse reactions listed above for the combination product, other undesirable effects previously reported with one of the individual components may be potential undesirable effects with CO-IRBECARD.

Irbesartan:

Cardiac disorders

Less frequent: ECG abnormalities

Musculoskeletal, connective tissue and bone disorders

Less frequent: extremity weakness

General disorders and administration site conditions

Less frequent: pruritus. abdominal (chest) pain

Hydrochlorothiazide:

Adverse events (regardless of relationship to medicine) reported with the use of hydrochlorothiazide alone include:

Blood and lymphatic system disorders:

Frequency unknown: aplastic anaemia. haemolytic anaemia, leucopenia, neutropenia/agranulocytosis, thrombocytopenia

Nervous system disorders:

Frequency unknown: paraesthesia, restlessness, vertigo

Eye disorders:

Frequency unknown: transient blurred vision, xanthopsia, acute myopia and secondary acute angle-closure glaucoma

Respiratory; thoracic and mediastinal disorders:

Frequency unknown: respiratory distress (Including pneumonitis and pulmonary oedema)

Gastrointestinal disorders:

Frequency unknown: anorexia, gastric irritation, diarrhoea, constipation, pancreatitis, sialadenitis

Hepato-biliary disorders:

Frequency unknown: jaundice (intrahepatic cholestatic jaundice)

Skin and subcutaneous tissue disorders:

Frequency unknown: anaphylactic reactions. toxic epidermal necrolysis, necrotizing angitis (vasculitis, cutaneous vasculitis), photosensitivity reactions, urticaria

Musculoskeletal, connective tissue and bone disorder:

Frequency unknown: muscle spasm, weakness

Renal and urinary disorders:

Frequency unknown: interstitial nephritis, renal dysfunction

General disorders and administration site conditions:

Frequency unknown: fever

Investigations:

Frequency unknown: electrolyte imbalance (including hyponatraemia and hypokalaemia), glycosuria, hyperglycaemia, hyperuricaemia

Laboratory test abnormalities: No clinically significant changes in laboratory test parameters occurred in controlled clinical studies. No special monitoring of laboratory parameters is necessary.

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. 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

No specific information is available on the treatment of overdosage with CO-IRBECARD. However, daily doses of irbesartan up to 900 mg/day for 8 weeks have been well tolerated.

The patient should be closely monitored and treatment should be symptomatic and supportive. Suggested measures include induction of emesis. CO-IRBECARD 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 anti-dysrhythmic medicine (e.g. sotalol) has also been administered, hypokalaemia may accentuate cardiac dysrhythmias.

The degree to which hydrochlorothiazide is removed by haemodialysis have not been established.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification:

A 7.1.3 Other hypotensives

Pharmacotherapeutic group: Angiotensin-II antagonists, plain.

ATC code: C09C A04.

Mechanism of action

CO-IRBECARD is a combination of an angiotensin-II receptor antagonist, irbesartan, and a thiazide diuretic, hydrochlorothiazide. The combination of these ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

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 8 500-fold) 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.

Hydrochlorothiazide is a benzothiadiazine (thiazide) diuretic with diuretic, natruretic 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 co-administration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with thiazide diuretics.

5.2 Pharmacokinetic properties

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

Absorption

Irbesartan and hydrochlorothiazide are orally active medicines and do not require biotransformation for their activity. Following oral administration of irbesartan and hydrochlorothiazide, the absolute oral bioavailability is 60-80 % and 50-80 % for irbesartan and hydrochlorothiazide, respectively. Food does not affect the bioavailability of irbesartan and hydrochlorothiazide. Peak plasma concentration occurs at 1.5-2 hours after oral administration for irbesartan and 1-2,5 hours for hydrochlorothiazide.

Distribution

Plasma protein binding of irbesartan is approximately 96 %, with negligible binding to cellular blood components. The volume of is 53-93 litres. Hydrochlorothiazide is 68 % protein-bound in the plasma, and its apparent volume of distribution is 3,6 - 7,8 litres/kg.

Biotransformation and elimination

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 is primarily oxidised by the cytochrome P450 enzyme CYP2C9; isoenzyme CYP3A4 has negligible effect.

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 the urine as unchanged irbesartan. Hydrochlorothiazide is not metabolised but is eliminated rapidly by the kidneys. The mean plasma half-life of hydrochlorothiazide reportedly range from 5 to 15 hours.

The terminal elimination half-life ($t_{1/2}$)of irbesartan is 11 to 15 hours. The total body clearance of intravenous administered irbesartan is 157 to 176 ml/min, of which 3,0 to 3,5 ml/nun is renal clearance.

Linearity/non-linearity

Irbesartan exhibits linear and dose proportional pharmacokinetics over the dose range. 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

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

In elderly (male and female normotensive subject (65 to 80 years) with clinically normal renal and hepatic function, the plasma AUC and peak plasma concentrations (C_{max} of irbesartan are approximately 20 % to 50 % greater than those observed in younger subjects (18 to 40 years).

Regardles of age, the elimination hall-life is comparable. No significant age·related differences in clinical effect have been observed. The area under the plasma concentratron time curve (AUC) for hydrochlorothyazide was elevated in the elderly group following multiple dosing coinsistent with previously published data.

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

Renal impairment: In patients with renal impairment (regardless of degree) or those undergoing haemodialysis, the pharmacokinetic parameters of irbesartan are not significantly altered. lrbesartan is not removed by haemodialysis. In patients with severe renal impairment (creatinine clearance < 20 ml/min), the elimination hall-life of hydrochlorothyazide was reported to increase to 21 hours.

Hepatic impairment: In patients with mild to moderate cirrhosis, the pharmacokinetic parameters of irbesartan are not significantly altered.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

150/12,5 mg; 300/12,5 mg & 300/25 mg tablets:

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

Film-coating: Hypromellose 6cP, titanium dioxide, purified stearic acid, microcrystalline cellulose, iron oxide yellow, iron oxide red, (iron oxide black (300/25 mg)).

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

2 years

6.4 Special precautions for storage

Store at or below 25 °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 white PVC/PCTFE/Aluminium foil and/or PVC/PE/PVDC/Aluminium blisters strips. The blister strips are packed in cartons containing 28 or 30 tablets.

Not all packing sizes may be marketed.

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

CO-IRBECARD 150/12,5 mg tablets: 47/7.1.3/0735

CO-IRBECARD 300/12,5 mg tablets: 47/7.1.3/0736

CO-IRBECARD 300/25 mg tablets: 47/7.1.3/0737

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22 February 2022

10 DATE OF REVISION OF THE TEXT

22 February 2022

COI/C/PI/A