Approved Professional Information for Medicines for Human Use:

ARBIN CO

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

ARBIN CO 150/12,5 mg tablets

ARBIN CO 300/12,5 mg tablets

ARBIN CO 300/25 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ARBIN CO 150/12,5 mg tablets

Each film-coated tablet contains 150 mg of irbesartan and 12,5 mg of hydrochlorothiazide.

ARBIN CO 300/12,5 mg tablets

Each film-coated tablet contains 300 mg of irbesartan and 12,5 mg of hydrochlorothiazide.

ARBIN CO 300/25 mg tablets

Each film-coated tablet contains 300 mg of irbesartan and 25 mg of hydrochlorothiazide.

Contains sugar.

ARBIN CO 150/12,5 mg: contains 26 mg of lactose monohydrate per tablet.

ARBIN CO 300/12,5 mg: contains 52 mg of lactose monohydrate per tablet.

ARBIN CO 300/25 mg: contains 52 mg of lactose monohydrate per tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

ARBIN CO 150/12,5 mg:

Light pink, oblong, biconvex film-coated tablets containing 150/12,5 mg of Irbesartan/Hydrochlorothiazide

ARBIN CO 300/12,5 mg:

Light pink, oblong, biconvex film-coated tablets containing 300/12,5 mg of Irbesartan/Hydrochlorothiazide

ARBIN CO 300/25 mg:

Red-brick, oblong, biconvex, film-coated tablets with a scoreline containing 300/25 mg of Irbesartan/Hydrochlorothiazide

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

ARBIN CO may also be used as initial therapy in previously untreated patients with sitting diastolic blood pressure of 110 mm Hg or higher, or in patients previously treated with one of the components of ARBIN CO whose diastolic blood pressure is 100 mm Hg or higher.

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

4.2 Posology and method of administration

Posology

ARBIN CO can be taken once daily, with or without food.

ARBIN CO 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 ARBIN CO alone, another antihypertensive medicine (e.g. beta-adrenergic blocking agent, long-acting calcium channel blocking agent) may be added.

Initial therapy:

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

ARBIN CO 300 mg/25 mg may be administered in patients insufficiently controlled by ARBIN CO 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, ARBIN CO 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, ARBIN CO 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 ARBIN CO. See section 4.4 – Hypotension – Volume depleted patients.

Paediatric population

Safety and efficacy in paediatric patients has not been established.

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to irbesartan, sulphonamide-derived medicines (e.g. thiazides) or to any of the ingredients of ARBIN CO.
- A history of angioedema related to previous therapy with ACE inhibitors or angiotensin receptor blockers (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).
- Bilateral renal artery stenosis.
- Renal artery stenosis in patients with a single 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. ARBIN CO) 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 ARBIN CO may lead to toxic blood concentrations of lithium (see section 4.5).
- Pregnancy and lactation (see section 4.6).
- The concomitant use of ARBIN CO with aliskiren-containing products is contraindicated (see section 4.4 and 4.5).
- Concomitantly using fluoroquinolones in moderate to severe renal impairment (creatinine clearance ≤ 30 mL/min), and in the elderly.
- Patients with a history of previous and/or current basal cell carcinomas and/or squamous cell carcinomas of the skin and lip.

4.4 Special warnings and precautions for use

Should a woman become pregnant while receiving ARBIN CO, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine (See section 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.

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 ARBIN CO and aliskiren is therefore contraindicated (see section 4.3). ARBIN CO should not be used concomitantly with aliskiren (see section 4.3).

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.

Intravascular Volume Depletion

ARBIN CO has been associated with symptomatic hypotension in hypertensive patients without other risk factors for hypotension. Symptomatic hypotension may be expected to 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 initiating therapy with ARBIN CO.

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 ARBIN CO, a similar effect should be anticipated. The use of ARBIN CO in patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney contraindicated (see section 4.3).

Renal impairment and kidney transplantation

When ARBIN CO 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 ARBIN CO in patients with a recent kidney transplantation. ARBIN CO 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.

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 ARBIN CO 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 (See section 4.3).

Primary aldosteronism

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

Metabolic and endocrine effects

Thiazide therapy may impair glucose tolerance. In diabetic patients dosage adjustments of insulin or oral hypoglycaemic agents 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 dose contained in ARBIN CO, 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 hypochloraemic alkalosis). Warning signs of fluid or electrolyte imbalance are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea or vomiting.

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 ARBIN CO 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 supplements or potassium-containing salts substitutes should be co-administered cautiously with ARBIN CO (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 may be evidence of hidden 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.

Lithium

The combination of lithium and ARBIN CO is not recommended (see sections 4.3 and 4.5).

Anti-doping test

Hydrochlorothiazide contained in this medicine could produce a positive analytic result in an anti-doping test.

General

In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with angiotensin converting enzyme inhibitors or angiotensin-II receptor antagonists that affect this system has been associated with acute hypotension, azotaemia, oliguria, or rarely acute renal failure (see section 4.5). As with any antihypertensive agent, 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 medicine or sulfonamide derivative medicine 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 in two epidemiological studies. Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC.

Patients taking ARBIN CO should be informed of the risk of NMS C 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 the case of exposure, adequate protection should be advised to the patients to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. ARBIN CO should not be used by patients who have had previous and/or current basal cell carcinomas and/or squamous cell carcinomas of the skin and/or lip (see section 4.3).

Lactose

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

4.5 Interaction with other medicines and other forms of interaction

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 section 4.3 and 4.4).

Other antihypertensive medicines

The antihypertensive effect of ARBIN CO may be increased with the concomitant use of other antihypertensive medicines. Irbesartan and hydrochlorothiazide (at doses up to 300 mg irbesartan/25 mg
hydrochlorothiazide) have been safely administered with other antihypertensive medicines including calcium channel blockers and beta-adrenergic blockers. Prior treatment with high dose diuretics may result in volume depletion and a risk of hypotension when initiating therapy with irbesartan with or without thiazide diuretics unless the volume depletion is corrected first (see section 4.4).

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors. Similar effects have been very rarely reported with irbesartan so far. Furthermore, renal clearance of lithium is reduced by thiazides so the risk of lithium toxicity could be increased with ARBIN CO. Therefore, the combination of lithium and ARBIN CO is not recommended (see sections 4.3 and 4.4).

Fluoroquinolones

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).

Medicine affecting potassium

The potassium-depleting effect of hydrochlorothiazide is attenuated by the potassium-sparing effect of irbesartan. However, this effect of hydrochlorothiazide on serum potassium would be expected to be potentiated by other medicine associated with potassium loss and hypokalaemia (e.g. other kaliuretic diuretics, laxatives, amphotericin, carbenoxolone, penicillin G sodium). Conversely, based on the experience with the use of other medicine that blunt the renin-angiotensin system, concomitant use of potassium-sparing diuretics (see section 4.3), potassium supplements, salt substitutes containing potassium or other medicine that may increase serum potassium levels (e.g. heparin sodium) may lead to increases in serum potassium. Adequate monitoring of serum potassium in patients at risk is recommended (see section 4.4).

Medicine affected by serum potassium disturbances

Periodic monitoring of serum potassium is recommended when ARBIN CO is administered with medicine affected by serum potassium disturbances (e.g. digitalis glycosides, antiarrhythmics).

Non-steroidal anti-inflammatory drugs

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

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

Additional information on irbesartan interactions

In clinical studies, the pharmacokinetic of irbesartan is not affected by hydrochlorothiazide. Irbesartan is mainly metabolised by CYP2C9 and to a lesser extent by glucuronidation. No significant pharmacokinetic or pharmacodynamic interactions were observed when irbesartan was co-administered with warfarin, a medicine metabolised by CYP2C9. The effects of CYP2C9 inducers such as rifampicin on the pharmacokinetic of irbesartan have not been evaluated. The pharmacokinetic of digoxin or simvastatin was not altered by co-administration of irbesartan.

Additional information on hydrochlorothiazide interactions

When administered concurrently, the following medicine may interact with thiazide diuretics:

Alcohol, barbiturate or narcotics: potentiation of orthostatic hypotension may occur;

Antidiabetic medicine (oral agents and insulins): dosage adjustment of the antidiabetic medicinal product may be required (see section 4.4);

Colestyramine and Colestipol resins: absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. ARBIN CO should be taken at least one hour before or four hours after these medications;

Corticosteroids, ACTH: electrolyte depletion, particularly hypokalaemia, may be increased;

Digitalis glycosides: thiazide induced hypokalaemia or hypomagnesaemia favour the onset of digitalis-induced cardiac arrhythmias (see section 4.4);

Non-steroidal anti-inflammatory drugs: the administration of a non-steroidal anti-inflammatory drug may reduce the diuretic, natriuretic and antihypertensive effects of thiazide diuretics in some patients;

Pressor amines (e.g. noradrenaline): the effect of pressor amines may be decreased, but not sufficiently to preclude their use;

Nondepolarizing skeletal muscle relaxants (e.g. tubocurarine): the effect of nondepolarizing skeletal muscle relaxants may be potentiated by hydrochlorothiazide;

Antigout medicine: dosage adjustments of antigout medicine may be necessary as hydrochlorothiazide may raise the level of serum uric acid. Increase in dosage of probenecid or sulfinpyrazone may be necessary. Co-administration of thiazide diuretics may increase the incidence of hypersensitivity reactions to allopurinol;
Calcium salts: thiazide diuretics may increase serum calcium levels due to decreased excretion. If calcium supplements or calcium sparing medicine (e.g. vitamin D therapy) must be prescribed, serum calcium levels should be monitored and calcium dosage adjusted accordingly;
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;
Other interactions: the hyperglycaemic effect of beta-blockers and diazoxide may be enhanced by thiazides. Anticholinergic medicines (e.g. atropine, beperiden) 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 medicine (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.

4.6 Fertility, pregnancy and lactation

Pregnancy & Breastfeeding

ARBIN CO is contraindicated in pregnancy and lactation (see sections 4.3 and 4.4).

Irbesartan

Safety in pregnancy and lactation has not been established (see section 4.3). When pregnancy is planned or confirmed ARBIN CO should be discontinued.

Medicines affecting the renin-angiotensin system, such as ARBIN CO, can cause embryonal toxicity, foetal and neonatal morbidity and mortality when administered to pregnant women.

Women of childbearing age should ensure effective contraception.

Hydrochlorothiazide

There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient. Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.

Since ARBIN CO contains hydrochlorothiazide, it is not recommended during pregnancy (see section 4.3). A switch to a suitable alternative treatment should be carried out in advance of a planned pregnancy.

Breastfeeding

Hydrochlorothiazide

Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production. The use of ARBIN CO during breastfeeding is contraindicated (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 (see section 5.3).

4.7 Effects on ability to drive and use machines

Based on its pharmacodynamic properties, ARBIN CO may 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

Irbesartan / Hydrochlorothiazide combination

Among 898 hypertensive patients who received various doses of irbesartan/hydrochlorothiazide, the most commonly reported ADRs were dizziness (5,6 %), fatigue (4,9 %), nausea/vomiting (1,8 %), and abnormal urination (1,4 %). In addition, increases in blood urea nitrogen (BUN) (2,3 %), creatine kinase (1,7 %) and creatinine (1,1 %) were also commonly observed in the trials.

The tables below show all adverse drug reactions (ADRs) observed during clinical trials and postmarket spontaneous reports with irbesartan:

Frequency estimate:

Frequent

Less frequent

Not known (cannot be estimated from the available data)

Table 1: Adverse Reactions in Placebo-Controlled Trials and Spontaneous Reports			
System Organ	**Frequency**		
Class	**Frequent**	**Less Frequent**	**Not known**

Immune system disorders			Cases of hypersensitivity reactions such as angioedema, rash, urticaria
Metabolism and nutrition disorders			Hyperkalaemia
Nervous system disorders	Dizziness	Orthostatic dizziness	Headache
Ear and labyrinth disorders			Tinnitus
Cardiac disorders		Syncope, hypotension, tachycardia, oedema	
Vascular disorders		Flushing	
Respiratory, thoracic and mediastinal disorders			Cough
Gastrointestinal disorders	Nausea / vomiting	Diarrhoea	Dyspepsia, dysgeusia

Hepatobiliary disorders		Jaundice	Hepatitis, abnormal liver function
Musculoskeletal and connective tissue disorders		Swelling extremity	Arthralgia, myalgia
Renal and urinary disorders	Abnormal urination		Impaired renal function including isolated cases of renal failure in patients at risk (see section 4.4)
Reproductive system and breast disorders		Sexual dysfunction, libido changes	
General disorders and administration site conditions	Fatigue		
Investigations	increases in blood urea nitrogen (BUN), creatinine and creatine kinase	decreases in serum potassium and sodium	

Additional information on individual components:

In addition to the adverse reactions listed above for the combination product, other adverse reactions previously reported with one of the individual components may be potential adverse reactions with ARBIN CO.

Table 2: Adverse reactions reported with the use of irbesartan alone			
System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Not known**
Blood and lymphatic system disorders			Thrombocytopenia
General disorders and administration site conditions		Chest pain	
Immune system disorders			Anaphylactic reaction including anaphylactic shock

Table 3: Adverse reactions reported with the use of hydrochlorothiazide alone			
System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Not known**

Investigations			Electrolyte imbalance (including hypokalaemia and hyponatraemia, see section 4.4), hyperuricaemia, glycosuria, hyperglycaemia, increases in cholesterol and triglycerides
Cardiac disorders			Cardiac arrhythmias
Blood and lymphatic system disorders			Aplastic anaemia, bone marrow depression, neutropenia/agranulocytosis, haemolytic anaemia, leucopenia, thrombocytopenia
Nervous system disorders			Vertigo, paraesthesia, light-headedness, restlessness
Eye disorders			Transient blurred vision, xanthopsia, acute myopia and secondary acute angle-closure glaucoma

Respiratory, thoracic and mediastinal disorders			Respiratory distress (including pneumonitis and pulmonary oedema)
Gastrointestinal disorders			Pancreatitis, anorexia, diarrhoea, constipation, gastric irritation, sialadenitis, loss of appetite
Renal and urinary disorders			interstitial nephritis, renal dysfunction
Skin and subcutaneous tissue disorders			Anaphylactic reactions, toxic epidermal necrolysis, necrotizing angitis (vasculitis, cutaneous vasculitis), cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, photosensitivity reactions, rash, urticaria

Musculoskeletal and connective tissue disorders			Weakness, muscle spasm
Vascular disorders			Postural hypotension
General disorders and administration site conditions			Fever
Hepatobiliary disorders			Jaundice (intrahepatic cholestatic jaundice)
Psychiatric disorders			Depression, sleep disturbances
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			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 also sections 4.4 and 5.1).

The dose dependent adverse events of hydrochlorothiazide (particularly electrolyte disturbances) may increase when titrating the hydrochlorothiazide.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reaction 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 overdose with ARBIN CO. However, daily doses of irbesartan up to 900 mg/day for 8 weeks have been well tolerated. The patient should be closely monitored, and the treatment should be symptomatic and supportive. Management depends on the time since ingestion and the severity of the symptoms. Suggested measures include induction of emesis. Serum electrolytes and creatinine should be monitored frequently. If hypotension occurs, the patient should be placed in a supine position, with salt and volume replacements given quickly. The most likely manifestations of irbesartan overdose are expected to be hypotension and tachycardia; bradycardia might also occur.

Overdose with hydrochlorothiazide is associated with electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration resulting from excessive diuresis. The most common signs and symptoms of overdose are nausea and somnolence. Hypokalaemia may result in muscle spasms and/or accentuate cardiac arrhythmias associated with the concomitant use of digitalis glycosides or certain anti-arrhythmic medicine.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological Classification/ Category and Class: A 7.13 Other hypotensives

Pharmacotherapeutic group: Angiotensin-II antagonists, combinations

ATC Code: C09DA04

Mechanism of action

Irbesartan

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 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 correct. It has no agonist activity at the AT_1 receptor, and a much greater affinity (more than 8 500 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 mEq/L) at the recommended doses. Irbesartan has no notable effects on serum triglycerides, cholesterol or glucose concentrations. There is no effect on serum uric or urinary acid excretion.

Hydrochlorothiazide

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 plasms 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 irbesartan.

Irbesartan and Hydrochlorothiazide are orally active agents and do not require biotransformation for their activity. Following oral administration of ARBIN CO, the absolute oral bioavailability is 60 to 80 % and 50 to 80 % for irbesartan and Hydrochlorothiazide respectively. Food does not affect the bioavailability of ARBIN CO.

Peak plasma concentration occurs at 1,5 to 2 hours after oral administration for irbesartan and 1 to 2,5 hours for Hydrochlorothiazide. Irbesartan is 90 % protein bound in the plasma, and has negligible binding to cellular components of blood. The volume of distribution is 53 to 93 litres. Hydrochlorothiazide is 68 % protein bound in the plasma, and its apparent volume of distribution is 3,6 – 7,8 litres / kg.

In plasma, unchanged irbesartan accounts for 80 to 85 % of the circulating radioactivity following oral or intravenous administration of ^{14}C irbesartan.

Irbesartan is metabolised by the liver via glucuronide conjugation and oxidation. The major circulation metabolite is irbesartan glucuronide (6 %). lrbesartan 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 drug metabolism (i.e. 1A1, 1A2, 2A6, 286, 206 or 2E1). lrbesartan does not induce or inhibit isoenzyme 3A4.

lrbesartan 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.

Hydrochlorothiazide is not metabolised and is eliminated by the kidneys. The mean plasma half-life of hydrochlorothiazide reportedly ranges 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 intravenously administered irbesartan is 157 to 176 mL/min, of which 3,0 to 3,5 mL/min is renal clearance.

lrbesartan 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.

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 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 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). Regardless of age, 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 $t_{1/2}$ of irbesartan are approximately 20 to 25 % greater in blacks than in whites; the peak plasma concentrations ($C_{max)}$ of irbesartan are 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

Irbesartan/hydrochlorothiazide

The potential toxicity of the irbesartan/hydrochlorothiazide combination after oral administration was evaluated in rats and macaques in studies lasting up to 6 months. There were no toxicological findings observed of relevance to human therapeutic use.

The following changes, observed in rats and macaques receiving the irbesartan/hydrochlorothiazide combination at 10/10 and 90/90 mg/kg/day, were also seen with one of the two medicines alone and/or were secondary to decreases in blood pressure (no significant toxicologic interactions were observed):

- kidney changes, characterized by slight increases in serum urea and creatinine, and hyperplasia/hypertrophy of the juxtaglomerular apparatus, which are a direct consequence of the interaction of irbesartan with the renin-angiotensin system
- slight decreases in erythrocyte parameters (erythrocytes, haemoglobin, haematocrit)
- stomach discoloration, ulcers and focal necrosis of gastric mucosa were observed in few rats in a 6 months toxicity study at irbesartan 90 mg/kg/day, hydrochlorothiazide 90 mg/kg/day, and irbesartan/hydrochlorothiazide 10/10 mg/kg/day. These lesions were not observed in macaques
- decreases in serum potassium due to hydrochlorothiazide and partly prevented when hydrochlorothiazide was given in combination with irbesartan.

Most of the above mentioned effects appear to be due to the pharmacological activity of irbesartan (blockade of angiotensin-II-induced inhibition of renin release, with stimulation of the renin-producing cells) and occur also with angiotensin converting enzyme inhibitors. These findings appear to have no relevance to the use of therapeutic doses of irbesartan/hydrochlorothiazide in humans.
No teratogenic effects were seen in rats given irbesartan and hydrochlorothiazide in combination at doses that produced maternal toxicity. The effects of the irbesartan/hydrochlorothiazide combination on fertility have not been evaluated in animal studies, as there is no evidence of adverse effect on fertility in animals or humans with either irbesartan or hydrochlorothiazide when administered alone. However, another angiotensin-II antagonist affected fertility parameters in animal studies when given alone. These findings were also observed with lower doses of this other angiotensin-II antagonist when given in combination with hydrochlorothiazide.
There was no evidence of mutagenicity or clastogenicity with the irbesartan/hydrochlorothiazide combination. The carcinogenic potential of irbesartan and hydrochlorothiazide in combination has not been evaluated in animal studies.

Irbesartan

There was no evidence of abnormal systemic or target organ toxicity at clinically relevant doses. In non-clinical safety studies, high doses of irbesartan (≥ 250 mg/kg/day in rats and ≥ 100 mg/kg/day in macaques) caused a reduction of red blood cell parameters (erythrocytes, haemoglobin, haematocrit). At very high doses (≥ 500 mg/kg/day) degenerative changes in the kidneys (such as interstitial nephritis, tubular distention, basophilic tubules, increased plasma concentrations of urea and creatinine) were induced by irbesartan in the rat and the macaque and are considered secondary to the hypotensive effects of the medicine which led to decreased renal perfusion. Furthermore, irbesartan induced hyperplasia/hypertrophy of the juxtaglomerular cells (in rats at ≥ 90 mg/kg/day, in macaques at ≥ 10 mg/kg/day). All of these changes were considered to be caused by the pharmacological action of irbesartan. For therapeutic doses of irbesartan in humans, the hyperplasia/hypertrophy of the renal juxtaglomerular cells does not
appear to have any relevance.

There was no evidence of mutagenicity, clastogenicity or carcinogenicity.

Fertility and reproductive performance were not affected in studies of male and female rats even at oral doses of irbesartan causing some parental toxicity (from 50 to 650 mg/kg/day), including mortality at the highest dose. No significant effects on the number of corpora lutea, implants, or live foetuses were observed. Irbesartan did not affect survival, development, or reproduction of offspring.

Studies in animals indicate that the radiolabelled irbesartan is detected in rat and rabbit foetuses. Irbesartan is excreted in the milk of lactating rats.

Animal studies with irbesartan showed transient toxic effects (increased renal pelvic cavitation, hydroureter or subcutaneous oedema) in rat foetuses, which were resolved after birth. In rabbits, abortion or early resorption was noted at doses causing significant maternal toxicity, including mortality. No teratogenic effects were observed in the rat or rabbit.

Hydrochlorothiazide

Although equivocal evidence for a genotoxic or carcinogenic effect was found in some experimental models, the extensive human experience with hydrochlorothiazide has failed to show an association between its use and an increase in neoplasms.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core

Croscarmellose sodium

Magnesium Stearate

Microcrystalline cellulose

Poloxamer 188

Pregelatinized starch

Film-coating

ARBIN CO 150 / 12,5 mg & ARBIN CO 300 / 12,5 mg:

Opadry pink 03A34089 consisting of Hypromellose 6cP, Iron Oxide yellow, Iron Oxide red, Microcrystalline cellulose, Purified stearic acid, Titanium dioxide.

ARBIN CO 300 / 25 mg:

Opadry pink 03A36005 consisting of Hypromellose 6cP, Iron Oxide red, Iron Oxide black, Microcrystalline cellulose, Purified stearic acid, Titanium dioxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C.

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

ARBIN CO is available in White PVC /PCTFE /Aluminium blisters packed into cardboard cartons in pack sizes of 30’s.

ARBIN CO is available in White PVC /PE /PVDC / Aluminium blisters packed into cardboard cartons in pack sizes of 30’s.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal <and other handling>

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd

1 Sherborne Road

Parktown

JOHANNESBURG

2193

South Africa

Tel: 0860287835

8. REGISTRATION NUMBER(S)

ARBIN CO 150/12,5 mg: 46/7.1.3/0658

ARBIN CO 300/12,5 mg: 46/7.1.3/0659

ARBIN CO 300/25 mg: 46/7.1.3/0660

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28 February 2022

10. DATE OF REVISION OF THE TEXT

03 August 2023