Package Insert for CO-IRBEWIN

SCHEDULING STATUS:

S3

PROPRIETARY NAME AND DOSAGE FORM:

CO-IRBEWIN® 150/12,5 tablets

CO-IRBEWIN® 300/12,5 tablets

COMPOSITION:

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

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

The other inactive ingredients are: croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, silicon dioxide and a film-coating.

Contains sugar (38,5 mg lactose monohydrate per CO-IRBEWIN 150/12,5 mg tablet and 89,5 mg lactose monohydrate per CO-IRBEWIN 300/12,5 mg tablet).

CATEGORY AND CLASS:

A 7.1.3 Other hypotensives.

PHARMACOLOGICAL ACTION:

Mechanism of Action

Irbesartan, an angiotensin receptor blocker (ARB), 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.

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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_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 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.

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Pharmacokinetic Properties

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

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 to 80 % and 50 to 80 % for irbesartan and hydrochlorothiazide, respectively. Food does not affect the bioavailability of irbesartan and hydrochlorothiazide.

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 approximately 96 % 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 circulating metabolite is irbesartan glucuronide (≈ 6 %). Irbesartan undergoes oxidation primarily by the cytochrome P450 isoenzyme CYP2C9; isoenzyme CYP3A4 has negligible effect. It is not metabolised by, nor does it substantially induce or inhibit most isoenzymes commonly associated with drug metabolism (i.e. CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2D6 or CYP2E1). Irbesartan does not induce or inhibit isoenzyme CYP3A4.

Irbesartan and its metabolites are excreted by both biliary and renal routes. About 20 % of the

administered radioactivity after an oral or intravenous dose of ^{14}C-irbesartan is recovered in urine with the remainder in the faeces. Less than 2 % of the dose is excreted in urine as unchanged irbesartan.

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 ($t_{½}$) 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.

Irbesartan exhibits linear pharmacokinetics over the therapeutic dose range. Steady-state plasma concentrations are attained within 3 days after initiation of a once-daily dosing regimen. Limited accumulation (< 20 %) is observed in plasma upon repeated once-daily dosing.

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, the elimination half-life is comparable. No significant age-related differences in clinical effect have been observed. The area under the plasma concentration time curve (AUC) for

hydrochlorothiazide was elevated in the elderly group following multiple dosing consistent with previously published data.

In black and white normotensive subjects, the plasma AUC and t½ of irbesartan are approximately 20 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.

INDICATIONS:

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

CO-IRBEWIN 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 CO-IRBEWIN whose diastolic blood pressure is 100 mm Hg or higher.

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

CONTRAINDICATIONS:

CO-IRBEWIN is contraindicated in patients with:

- Hypersensitivity to irbesartan, sulphonamide-derived medicines (e.g. thiazides), or to any other component of the CO-IRBEWIN formulation. 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).
- 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.
- Porphyria – hydrochlorthiazide has been associated with acute attacks of porphyria.
- Thiazide diuretics in (fixed dose) combination with irbesartan (i.e. CO-IRBEWIN) 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-IRBEWIN may lead to toxic blood concentrations of lithium.
- Pregnancy and lactation (See HUMAN REPRODUCTION)
- Do not co-administer CO-IRBEWIN with aliskiren-containing medicines in patients with diabetes or with moderate to severe renal impairment (glomerular filtration rate [GFR] <

60 ml/min/1,73 m^2).

- Do not co-administer CO-IRBEWIN with Angiotensin-Converting Enzyme Inhibitors (ACEIs) in patients with diabetic nephropathy.
- Concomitant use of angiotensin receptor blockers, such as CO-IRBEWIN, with fluoroquinolones is contraindicated in patients with moderate to severe renal impairment.

Paediatric Use:

Safety and effectiveness in paediatric patients have not been established.

WARNINGS and SPECIAL PRECAUTIONS:

If a woman is contemplating pregnancy, or becomes pregnant while receiving CO-IRBEWIN, treatment should be stopped promptly and switched to a medicine safe to use in pregnancy.

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 fetus to unnecessary hazard, including fetal or neonatal jaundice, thrombocytopenia and possibly other adverse reactions, which have occurred in the adult.

Non-melanoma skin cancer:

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

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

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Special attention is advised in patients with known risk factors of skin cancer such as: skin phototypes I and II (pale white and fair skin), family history of skin cancer, history of skin damage due to sun/UV radiation and radiotherapy exposure, smoking and photosensitizing treatment. Possible preventative measures such as limited exposure to sunlight and ultraviolet rays and adequate protection when exposed to sunlight 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 non-melanoma skin and lip cancer (see SIDE EFFECTS (Individual component – HCTZ) – Neoplasms benign, malignant and unspecified (including cysts and polyps)).

Photosensitivity:

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

If photosensitivity reactions occur during treatment with hydrochlorothiaizde medicines, treatment should be stopped.

Hypotension - Volume Depleted Patients:

CO-IRBEWIN 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-IRBEWIN. Thiazides may potentiate the action of other antihypertensive medicines (see INTERACTIONS).

Dual Blockade of the Renin-Angiotensin-Aldosterone System (RAAS) with aliskiren containing medicines:

Dual blockade of the RAAS by combining CO-IRBEWIN with an angiotensin-converting enzyme inhibitor (ACEI) or aliskiren is not recommended since there is an increased risk of hypotension, hyperkalemia, and changes in renal function.

The use of CO-IRBEWIN in combination with aliskiren is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1,73 m^2) – see CONTRAINDICATIONS.

The use of CO-IRBEWIN in combination with an ACEI is contraindicated in patients with diabetic nephropathy (see CONTRAINDICATIONS).

General: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function during therapy with CO-IRBEWIN may be anticipated in susceptible individuals. In patients whose renal function depends on the activity of the renin-angiotensin-aldosterone system (e.g. hypertensive patients with renal artery stenosis in one or both kidneys, or patients with severe congestive heart failure), treatment with other medicines that affect this system has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. The possibility of a similar effect occurring with the use of an angiotensin II receptor antagonist, including CO-IRBEWIN, cannot be excluded (see CONTRA-INDICATIONS).

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

Impaired Hepatic and Renal Function:

CO-IRBEWIN is contraindicated in patients with severe renal disease (creatinine clearance < 30 ml/min) (see CONTRA-INDICATIONS). Hydrochlorothiazide-associated precipitation of azotemia may occur in patients with impaired renal function.

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

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

Hyperuricaemia may occur, and an acute attack of gout may be precipitated in certain patients receiving thiazide therapy. Insulin requirements in diabetic patients may be increased and latent diabetes mellitus may become manifest during thiazide administration. Increases in cholesterol and triglyceride levels have been associated with thiazide diuretic therapy; however, minimal or no effects were reported at the 12,5 mg hydrochlorothiazide dose contained in CO-IRBEWIN.

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

Signed:

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

Use in the elderly: In clinical studies there was no age-related difference in efficacy or safety profile of irbesartan.

Secondary Acute Angle-Closure Glaucoma and/or Acute Myopia: Hydrochlorothiazide is a sulphonamide. Sulfonamide or sulphonamide derivative medicines can cause an idiosyncratic reaction, which may result in secondary acute angle-closure glaucoma and/or acute myopia. 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 sulphonamide or penicillin allergy.

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

Fluoroquinolones and angiotensin receptor blockers (ARBs): Concomitant use of fluoroquinolones and ARBs, such as CO-IRBEWIN, may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients (see CONTRAINDICATIONS). Renal function should be assessed before initiating treatment and monitored during treatment with fluoroquinolones or ARBs whether used separately and/or concomitantly.

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

Lactose intolerance:

CO-IRBEWIN contains lactose and should be used with caution in patients with intolerance to some sugars (e.g. lactose).

INTERACTIONS:

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

Irbesartan is primarily metabolised by CYP2C9, however, during clinical interactions studies, no significant pharmacokinetic and pharmacodynamic 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 are 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 with irbesartan may lead to increases in serum potassium. Concurrent therapy with hydrochlorothiazide may reduce the frequency of this effect.

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

Antidiabetic 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-IRBEWIN should be taken at least one hour before or four hours after these medications.

Lithium – Increases in serum lithium concentrations and lithium toxicity have been reported with concomitant use of irbesartan.

Diuretic medicines reduce the renal clearance of lithium and increase the risk of lithium toxicity. Coadministration with CO-IRBEWIN should be approached with caution and the frequent monitoring of serum lithium levels is recommended.

Inhibitors of Endogenous Prostaglandin Synthesis (i.e. non-steroidal anti-inflammatory medicines) - In some patients, these medicines can reduce the effects of thiazide diuretics.

Other diuretics and antihypertensive medications - The thiazide component of CO-IRBEWIN may potentiate the actions of other antihypertensive medicines, especially ganglionic or peripheral adrenergic-blocking medicines. Hydrochlorothiazide 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.

The combination of CO-IRBEWIN with aliskiren-containing medicines is contraindicated in patients with diabetes mellitus or moderate to severe renal impairment (GFR < 60 ml/min/1,73 m^2) and is not recommended in other patients.

Angiotensin-converting enzyme inhibitors (ACEIs): The use of CO-IRBEWIN in combination with an ACEI is contraindicated in patients with diabetic nephropathy and is not recommended in other patients (see CONTRAINDICATIONS).

Signed:

Non-Steroidal Anti-Inflammatory Medicines including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors) – In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, coadministration of NSAIMs, including selective COX-2 inhibitors, with angiotensin II receptor antagonists, including irbesartan, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving irbesartan and NSAIM therapy. The antihypertensive effect of angiotensin II receptor antagonists, including irbesartan, may be attenuated by NSAIMs including selective COX-2 inhibitors.

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.

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 CONTRAINDICATIONS).

HUMAN REPRODUCTION:

Pregnancy:

CO-IRBEWIN is contraindicated in pregnancy (see CONTRAINDICATIONS and WARNINGS and SPECIAL PRECAUTIONS).

CO-IRBEWIN can cause fetal morbidity and death. CO-IRBEWIN passes through the placenta and can be presumed to cause disturbances in fetal blood pressure regulatory mechanisms. Oligohydramnios, as well as hypotension, oliguria and anuria in newborns have been reported after administration of ARBs such as CO-IRBEWIN 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 adequate contraception while taking CO-IRBEWIN.

Lactation:

CO-IRBEWIN is contraindicated in lactation (see CONTRAINDICATIONS and WARNINGS AND SPECIAL PRECAUTIONS).

DOSAGE AND DIRECTIONS FOR USE:

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

One tablet daily (with or without food).

CO-IRBEWIN 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-IRBEWIN 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-IRBEWIN 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.

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-IRBEWIN is not recommended for patients with severe renal dysfunction (creatinine clearance < 30 ml/min) (see Special Precautions - Impaired Hepatic and Renal Function).

No dosage reduction is generally necessary in patients with mild to moderate hepatic impairment. Due to the hydrochlorothiazide component, CO-IRBEWIN should be used with caution in patients with severe hepatic impairment (see Special Precautions - Impaired Hepatic and Renal Function).

Patients with Intravascular Volume Depletion:

Volume and/or sodium depletion should be corrected prior to administration of CO-IRBEWIN (see WARNINGS and SPECIAL PRECAUTIONS - Hypotension - Volume depleted patients).

SIDE EFFECTS:

The frequency of adverse reactions listed below is defined using the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1 000, < 1/100); rare (≥ 1/10 000, < 1/1 000); very rare (< 1/10 000), including isolated reports.

Irbesartan/hydrochlorothiazide combination:

Immune system disorders:

Uncommon: rash

Nervous system disorders:

Common: dizziness, headache

Uncommon: orthostatic hypotension

Cardiac disorders:

Uncommon: hypotension, oedema, syncope, tachycardia

Vascular disorders:

Uncommon: flushing

Gastrointestinal disorders:

Common: nausea/vomiting

Uncommon: diarrhoea, dry mouth

Musculoskeletal, connective tissue and bone disorders:

Uncommon: swelling of the extremities, muscle/skeletal pain

Renal and urinary disorders:

Common: abnormal urination

Reproductive system and breast disorders:

Uncommon: libido changes, sexual dysfunction

General disorders and administration site conditions:

Common: fatigue

Uncommon: weakness

In addition, since introduction of CO-IRBEWIN in the market the following adverse reactions have also been reported:

Immune system disorders:

Cases of hypersensitivity reactions (angioedema, urticarial, anaphylactic reactions including anaphylactic shock) have been reported.

Metabolism and nutrition disorders:

Hyperkalaemia

Respiratory, thoracic and mediastinal disorders:

Cough

Gastrointestinal disorders:

Dyspepsia

Hepato-biliary 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

Blood and lymphatic system disorders:

Frequency unknown: thrombocytopenia (including thrombocytopenic purpura)

Skin and subcutaneous tissue disorders:

Frequency unknown: psoriasis (and psoriasis exacerbation) (see WARNINGS and SPECIAL PRECAUTIONS), photosensitivity

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-IRBEWIN.

Irbesartan:

Cardiac disorders:

Uncommon: ECG abnormalities

Musculoskeletal, connective tissue and bone disorders:

Uncommon: extremity weakness

General disorders and administration site conditions:

Uncommon: pruritus, abdominal (chest) pain

Hydrochlorothiazide:

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

Neoplasms benign, malignant and unspecified (including cysts and polyps):

The following side effects have been reported and the frequencies are unknown: non-melanoma skin and lip cancer (Basal Cell Carinoma and Squamous Cell Carcinoma)

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

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 disorders:

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.

KNOWN SYMPTOMS OF OVER-DOSAGE AND PARTICULARS OF ITS TREATMENT:

No specific information is available on the treatment of overdosage with CO-IRBEWIN. However, daily doses of irbesartan up to 900 mg/day for 8 weeks were well tolerated. The patients should be closely monitored and treatment should be symptomatic and supportive, including fluid and electrolyte replacement. Suggested measures include induction of emesis and/or gastric lavage. Irbesartan is not removed from the body by haemodialysis.

The most common signs and symptoms observed in adults exposed to hydrochlorothiazide are those caused by electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration resulting from excessive diuresis. If a cardiac glycoside (e.g. digoxin) or other anti-dysrhythmic medicines (e.g. sotalol) has also been administered, hypokalaemia may accentuate cardiac dysrhythmias.

Signed:

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

IDENTIFICATION:

CO-IRBEWIN 150/12,5: peach (orange-pink) coloured, biconvex, oval, film-coated tablet, engraved with a heart on one side and “2875” on the other side.

CO-IRBEWIN 300/12,5: peach (orange-pink) coloured, biconvex, oval, film-coated tablet, engraved with a heart on one side and “2876” on the other side.

PRESENTATION:

CO-IRBEWIN 150/12,5 and CO-IRBEWIN 300/12,5 tablets are packed in PVC/PVDC/Aluminium foil blister packs containing 28 or 30 tablets.

STORAGE INSTRUCTIONS:

Store in a dry place, at or below 25 °C.

KEEP OUT OF REACH OF CHILDREN.

Keep blister in carton until required for use.

REGISTRATION NUMBERS:

CO-IRBEWIN 150/12,5: A40/7.1.3/0290

CO-IRBEWIN 300/12,5: A40/7.1.3/0291 (SN.2023.05 REG NR INCORRECT) 0287

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Zentiva South Africa (Pty) Ltd

2 Bond Street

Signed:

Midrand, 1685

South Africa

DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION:

Registration date: 18 April 2008

Approved (revised) by the Authority: 31 July 2019

Signed: