IRBESARTAN / HYDROCHLOROTHIAZIDE

COAPROVEL
150 mg / 12.5 mg Film-Coated Tablet
300 mg / 12.5 mg Film-Coated Tablet
300 mg / 25 mg Film-Coated Tablet

sanofi

Antihypertensive

Formulation
Each Irbesartan / Hydrochlorothiazide (CoAprovel) 150 mg / 12.5 mg film-coated tablet contains
Irbesartan, Ph.Eur. ……150 mg
Hydrochlorothiazide, Ph.Eur. ……..12.5 mg

Each Irbesartan / Hydrochlorothiazide (CoAprovel) 300 mg / 12.5 mg film-coated tablet contains
Irbesartan, Ph.Eur. ……300 mg
Hydrochlorothiazide, Ph.Eur. ……..12.5 mg

Each Irbesartan / Hydrochlorothiazide (CoAprovel) 300 mg / 25 mg film-coated tablet contains
Irbesartan, Ph.Eur. ……300 mg
Hydrochlorothiazide, Ph.Eur. ……..25 mg

Pharmaceutical Form
Irbesartan / Hydrochlorothiazide (CoAprovel) 150 mg / 12.5 mg film-coated tablets
Peach, biconvex, oval-shaped, with a heart debossed on one side and the number 2875 engraved on the other side.

Irbesartan / Hydrochlorothiazide (CoAprovel) 300 mg / 12.5 mg film-coated tablets
Peach, biconvex, oval-shaped, with a heart debossed on one side and the number 2876 engraved on the other side.

Irbesartan / Hydrochlorothiazide (CoAprovel) 300 mg / 25 mg film-coated tablets
Pink, biconvex, oval-shaped, with a heart debossed on one side and the number 2788 engraved on the other side.

Indication
Irbesartan / Hydrochlorothiazide (CoAprovel) is indicated for the treatment of hypertension.
It may be used either alone or in combination with other antihypertensive agents (e.g., beta-adrenergic blocking agent, long-acting calcium-channel blocking agent).
Irbesartan / Hydrochlorothiazide (CoAprovel) may also be used as initial therapy in patients who are likely to need multiple drugs to achieve their blood pressure goals.

Dosage and Administration
General:
In patients whose blood pressure is not adequately controlled with Irbesartan 300 mg monotherapy, Irbesartan / Hydrochlorothiazide (CoAprovel) 300 mg / 12.5 mg once daily may be administered, with or without food.
Irbesartan / Hydrochlorothiazide (CoAprovel) 150 mg / 12.5 mg may be initiated in patients who are not adequately controlled with Hydrochlorothiazide, or Irbesartan 150 mg alone.
Patients not responding adequately to Irbesartan / Hydrochlorothiazide (CoAprovel) 150 mg / 12.5 mg can have the dose increased to Irbesartan / Hydrochlorothiazide (CoAprovel) 300 mg / 12.5 mg. Doses higher than Irbesartan / Hydrochlorothiazide 300 mg / 25 mg are not recommended.
If blood pressure is not adequately controlled with Irbesartan / Hydrochlorothiazide (CoAprovel) alone,

another antihypertensive drug (eg, beta-adrenergic blocking agent, long-acting calcium channel blocking agent) may be added.

Initial Therapy: The usual starting dose for initial therapy with Irbesartan / Hydrochlorothiazide (CoAprovel) is 150 mg / 12.5 mg once daily. The dosage can be increased after 1 to 2 weeks of therapy to a maximum of one 300 mg / 25 mg tablet once daily as needed to control blood pressure.

Special Populations:
Pediatric patients
Safety and effectiveness in pediatric patients have not been established.

Elderly patients
No dosage reduction is generally necessary in the elderly.
Among patients who received Irbesartan / Hydrochlorothiazide (CoAprovel) in clinical studies, no overall differences in efficacy or safety were observed between older patients (65 years or older) and younger patients.

Hepatic impairment
No dosage reduction is generally necessary in patients with mild to moderate hepatic impairment. Due to the Hydrochlorothiazide component, Irbesartan / Hydrochlorothiazide (CoAprovel) should be used with caution in patients with severe hepatic impairment (see section Warnings).

Renal impairment
No dosage reduction is generally necessary in patients with mild-to-moderate renal impairment (creatinine clearance > 30 mL/min). However, due to the Hydrochlorothiazide component, Irbesartan / Hydrochlorothiazide (CoAprovel) is not recommended for patients with severe renal impairment (creatinine clearance ≤ 30 mL/min) (see section Warnings).

Patients with intravascular volume depletion
In severely volume-depleted and/or sodium-depleted patients, such as those treated vigorously with diuretics, the condition should be corrected prior to administration of Irbesartan / Hydrochlorothiazide (CoAprovel) (see section Warnings).

Contraindications
Irbesartan / Hydrochlorothiazide (CoAprovel) is contraindicated in patients who are hypersensitive to Irbesartan, sulfonamide derived drugs (eg, thiazides), or to any other component of the Irbesartan / Hydrochlorothiazide (CoAprovel) formulation. In general, hypersensitivity reactions are more likely to occur in patients with a history of allergy or bronchial asthma. Irbesartan / Hydrochlorothiazide (CoAprovel) is contraindicated in patients who are anuric.

Do not co-administer Irbesartan / Hydrochlorothiazide (CoAprovel) 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 Irbesartan / Hydrochlorothiazide (CoAprovel) with Angiotensin-Converting Enzyme Inhibitors (ACEIs) in patients with diabetic nephropathy.

Warnings
Hypotension - Volume-Depleted Patients
Irbesartan / Hydrochlorothiazide (CoAprovel) has been rarely associated with hypotension in hypertensive patients without other risk factors for hypotension. Symptomatic hypotension may be expected to occur in patients who develop sodium or volume-depletion. Volume and/or sodium-depletion should be corrected before initiating therapy with Irbesartan / Hydrochlorothiazide (CoAprovel).

Thiazides may potentiate the action of other antihypertensive drugs (see section Interactions).

Fetal/Neonatal Morbidity and Mortality
Although there is no experience with Irbesartan / Hydrochlorothiazide (CoAprovel) in pregnant women, in utero exposure to ACE inhibitors given to pregnant women during the second and third trimesters has been reported to cause injury and death to the developing fetus. Thus, as for any drug that also acts directly on the renin-angiotensin-aldosterone system, Irbesartan / Hydrochlorothiazide (CoAprovel) should not be used during pregnancy. If pregnancy is detected during therapy, Irbesartan / Hydrochlorothiazide (CoAprovel) should be discontinued as soon as possible.

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.

Impaired Hepatic and Renal Function
Irbesartan / Hydrochlorothiazide (CoAprovel) is not recommended for patients with severe renal impairment (creatinine clearance ≤ 30 mL/min) (see section Contraindications). Hydrochlorothiazide-associated precipitation of azotemia may occur in patients with impaired renal function. Irbesartan / Hydrochlorothiazide (CoAprovel) 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 HCTZ, can cause fluid or electrolyte imbalance (hypokalemia, hyponatremia and hypochloremic alkalosis). Although hypokalemia may develop when thiazide diuretics are used alone, especially with higher doses, concurrent therapy with Irbesartan reduces the frequency of diuretic-induced hypokalemia. 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 hypercalcemia 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 hypomagnesemia.

Hyperuricemia 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. Irbesartan may induce hypoglycaemia, particularly in diabetic patients. In patients treated with insulin or antidiabetics an appropriate blood glucose monitoring should be considered; a dose adjustment of insulin or antidiabetics may be required when indicated (see section Interactions). 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 Irbesartan / Hydrochlorothiazide (CoAprovel). Monitoring of laboratory parameters may be necessary in patients at risk for electrolyte and metabolic disturbances.

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

Choroidal effusion, Secondary Acute Angle-Closure Glaucoma and/or Acute Myopia
Hydrochlorothiazide is a sulfonamide. Sulfonamide, or sulfonamide derivative, drugs can cause an idiosyncratic reaction, which may result in choroidal effusion with visual field defect, secondary acute angle-closure glaucoma and/or acute myopia.

Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours

to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug intake as rapidly as possible.

Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

Excipients:
Irbesartan / Hydrochlorothiazide (CoAprovel) film-coated tablet contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Irbesartan / Hydrochlorothiazide (CoAprovel) film-coated tablet contains sodium. This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

Non-melanoma skin cancer
An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of Hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. 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.

Acute Respiratory Toxicity
Very rare severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS) have been reported after taking Hydrochlorothiazide. Pulmonary oedema typically develops within minutes to hours after Hydrochlorothiazide intake. At the onset, symptoms include dyspnoea, fever, pulmonary deterioration and hypotension. If diagnosis of ARDS is suspected, Irbesartan / Hydrochlorothiazide (CoAprovel) should be withdrawn and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following Hydrochlorothiazide intake.

Precautions
Dual Blockade of the Renin-Angiotensin-Aldosterone System (RAAS): Dual blockade of the RAAS by combining Irbesartan / Hydrochlorothiazide (CoAprovel) with an angiotensin-converting enzyme inhibitor (ACEI) or with aliskiren is not recommended since there are increased risks of hypotension, hyperkalemia, and changes in renal function.

The use of Irbesartan / Hydrochlorothiazide (CoAprovel) in combination with aliskiren is contraindicated in patients with diabetes mellitus or with renal impairment (GFR < 60 ml/min/1.73 m^2) (see section Contraindications and section Interactions).

The use of Irbesartan / Hydrochlorothiazide (CoAprovel) in combination with an ACEI is contraindicated in patients with diabetic nephropathy (see section Contraindications and section Interactions).

The use of Irbesartan / Hydrochlorothiazide (CoAprovel) in patients with psoriasis or a history of psoriasis should be carefully weighed as it may exacerbate psoriasis.

General: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function during therapy with Irbesartan / Hydrochlorothiazide (CoAprovel) may be anticipated in susceptible individuals. In patients whose renal function depends on the activity of the renin-angiotensin-aldosterone system (eg, hypertensive patients with renal artery stenosis in one or both kidneys, or patients with severe congestive heart failure), treatment with drugs that affect this system has been associated with oliguria and/or progressive 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 Irbesartan / Hydrochlorothiazide (CoAprovel), cannot be excluded.

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

Interactions
Based on in vitro data, no interactions with Irbesartan would be expected to occur with drugs whose metabolism is dependent upon cytochrome P450 isoenzymes CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2D6, CYP2E1 or CYP3A4. Irbesartan is primarily metabolized by CYP2C9, however, during clinical interaction studies, no significant pharmacokinetic and pharmacodynamic interactions were observed when Irbesartan was co-administered with warfarin (a drug metabolized by CYP2C9). Irbesartan does not affect the pharmacokinetics of digoxin or simvastatin. The pharmacokinetics of Irbesartan are not affected by coadministration with nifedipine or Hydrochlorothiazide.

The combination of Irbesartan / Hydrochlorothiazide (CoAprovel) with aliskiren-containing medicinal products 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 (see section Contraindications and section Precautions).

Angiotensin-converting enzyme inhibitors (ACEIs)
The use of Irbesartan / Hydrochlorothiazide (CoAprovel) in combination with an ACEI is contraindicated in patients with diabetic nephropathy and is not recommended in other patients (see section Contraindications and section Precautions).

Based on experience with the use of other drugs that affect the renin-angiotensin system, concomitant use of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicinal products that may increase kalaemia with Irbesartan may lead to increases in serum potassium, sometimes severe, and requires close monitoring of serum potassium. Concurrent therapy with Hydrochlorothiazide may reduce the frequency of this effect.

Non-Steroidal Anti-Inflammatory Agents 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 NSAIDs, 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 NSAID therapy. The antihypertensive effect of angiotensin II receptor antagonists, including Irbesartan, may be attenuated by NSAIDs including selective COX-2 inhibitors.

Repaglinide: Irbesartan has the potential to inhibit OATP1B1. In a clinical study, it was reported that Irbesartan increased the C_{max} and AUC of repaglinide (substrate of OATP1B1) by 1.8-fold and 1.3-fold, respectively, when administered 1 hour before repaglinide. In another study, no relevant pharmacokinetic interaction was reported, when the two drugs were co-administered. Therefore, dose adjustment of antidiabetic treatment such as repaglinide may be required (see section Warnings).

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

Antidiabetic drugs (oral agents and insulin)
Thiazides may elevate blood glucose levels, thus, dosage adjustments of antidiabetic agents may be necessary.

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

Cardiac glycosides (eg, digoxin) and other antiarrhythmic drugs (eg, sotalol)
Diuretic-induced hypokalemia may accentuate cardiac arrhythmias.

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

Cholestyramine resin and colestipol HCL
May delay or decrease absorption of HCTZ. Irbesartan / Hydrochlorothiazide (CoAprovel) should be taken at least one hour before or four hours after these mediations.

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

Diuretic agents reduce the renal clearance of lithium and increase the risk of lithium toxicity. Coadministration with Irbesartan / Hydrochlorothiazide (CoAprovel) should be approached with caution and the frequent monitoring of serum lithium levels is recommended.

Inhibitors of Endogenous Prostaglandin Synthesis (ie, NSAIDs)
In some patients, these agents can reduce the effects of thiazide diuretics.

Other diuretics and antihypertensive medications
The thiazide component of Irbesartan / Hydrochlorothiazide (CoAprovel) may potentiate the actions of other antihypertensive drugs, especially ganglionic or peripheral adrenergic-blocking drugs. HCTZ may interact with diazoxide; blood glucose, serum uric acid levels and blood pressure should be monitored.

Drugs used during surgery
The effects of nondepolarizing muscle relaxants, preanesthetics and anesthetics used in surgery (e.g., tubocurarine) may be potentiated by HCTZ; dosage adjustments may be required. Preanesthetic and anesthetic agents should be given in reduced dosage, and if possible, HCTZ therapy discontinued one week prior to surgery.

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

Pregnancy
When pregnancy is detected, Irbesartan / Hydrochlorothiazide (CoAprovel) should be discontinued as soon as possible (see section Warnings).

Lactation
Irbesartan is excreted in the milk of lactating rats. It is not known whether Irbesartan or its metabolites

are excreted in human milk. Hydrochlorothiazide is excreted in human breast milk. Thiazides in high doses causing intense diuresis can inhibit the milk production. The use of Irbesartan / Hydrochlorothiazide (CoAprovel) during breastfeeding is not recommended. Because of the potential risk to the infant, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of Irbesartan / Hydrochlorothiazide (CoAprovel) to the therapy of the mother.

Driving a Vehicle or Performing Other Hazardous Tasks

The effects of Irbesartan / Hydrochlorothiazide (CoAprovel) on the ability to drive motor vehicles or operate machinery have not been specifically studied, but based on its pharmacodynamic properties, Irbesartan / Hydrochlorothiazide (CoAprovel) 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.

Adverse Reactions

Irbesartan/Hydrochlorothiazide combination

Among 898 hypertensive patients who received various doses of Irbesartan / Hydrochlorothiazide (range: 37.5 mg / 6.25 mg to 300 mg / 25 mg) in placebo-controlled trials, 29.5% of the patients experienced adverse reactions. 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.

Table 1 gives the adverse reactions observed from spontaneous reporting and in placebo-controlled trials.

The frequency of adverse reactions listed below is defined using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: Adverse Reactions in Placebo-Controlled Trials and Spontaneous Reports

Investigations:	Common: Uncommon:	increases in blood urea nitrogen (BUN), creatinine and creatine kinase decreases in serum potassium and sodium
Cardiac disorders:	Uncommon:	syncope, hypotension, tachycardia, oedema
Nervous system disorders:	Common: Uncommon: Not known:	dizziness orthostatic dizziness headache
Ear and labyrinth disorders:	Not known:	tinnitus
Respiratory, thoracic and mediastinal disorders:	Not known:	cough
Gastrointestinal disorders:	Common: Uncommon: Not known:	nausea/vomiting diarrhoea dyspepsia, dysgeusia
Renal and urinary disorders:	Common: Not known:	abnormal urination impaired renal function including isolated cases of renal failure in patients at risk
Musculoskeletal and connective tissue disorders:	Uncommon: Not known:	swelling extremity arthralgia, myalgia

Metabolism and nutrition disorders:	Not known:	hyperkalaemia
Vascular disorders:	Uncommon:	flushing
General disorders and administration site conditions:	Common:	fatigue
Immune system disorders:	Not known:	cases of hypersensitivity reactions such as angioedema, rash, urticaria
Hepatobiliary disorders:	Uncommon: Not known:	jaundice hepatitis, abnormal liver function
Reproductive system and breast disorders:	Uncommon:	sexual dysfunction, libido changes

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 Irbesartan / Hydrochlorothiazide (CoAprovel). Tables 2 and 3 below detail the adverse reactions reported with the individual components of Irbesartan / Hydrochlorothiazide (CoAprovel).

Table 2: Adverse reactions reported with the use of Irbesartan alone

Blood and lymphatic system disorders:	Not known:	anaemia, thrombocytopenia
General disorders and administration site conditions:	Uncommon:	chest pain
Immune system disorders:	Not known:	Anaphylactic reaction including anaphylactic shock
Metabolism and nutrition disorders:	Not known:	hypoglycemia

Table 3: Adverse reactions reported with the use of Hydrochlorothiazide alone

Investigations:	Not known:	electrolyte imbalance (including hypokalaemia and hyponatraemia), hyperuricaemia, glycosuria, hyperglycaemia, increases in cholesterol and triglycerides
Cardiac disorders:	Not known:	cardiac arrhythmias
Blood and lymphatic system disorders:	Not known:	aplastic anaemia, bone marrow depression, neutropenia/agranulocytosis, haemolytic anaemia, leucopenia, thrombocytopenia
Nervous system disorders:	Not known:	vertigo, paraesthesia, light-headedness, restlessness
Eye disorders:	Not known:	transient blurred vision, xanthopsia, acute myopia and secondary acute angle-closure glaucoma, choroidal effusion
Respiratory, thoracic and mediastinal disorders:	Very rare: Not known:	acute respiratory distress syndrome (ARDS) (see section Warnings) respiratory distress (including pneumonitis and pulmonary oedema)
Gastrointestinal disorders:	Not known:	pancreatitis, anorexia, diarrhoea, constipation, gastric irritation, sialadenitis, loss of appetite

Renal and urinary disorders:	Not known:	interstitial nephritis, renal dysfunction
Skin and subcutaneous tissue disorders:	Not known:	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:	Not known:	weakness, muscle spasm
Vascular disorders:	Not known:	postural hypotension
General disorders and administration site conditions:	Not known:	fever
Hepatobiliary disorders:	Not known:	jaundice (intrahepatic cholestatic jaundice)
Psychiatric disorders:	Not known:	depression, sleep disturbances
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Not known:	non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma)

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose dependent association between HCTZ and NMSC has been observed (see also section Warnings and section Pharmacological Properties).

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

Overdose and Treatment

Signs and Symptoms

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

Management

Experience in adults exposed to Irbesartan doses of up to 900 mg/day for 8 weeks revealed no toxicity. No specific information is available on the treatment of overdosage with Irbesartan / Hydrochlorothiazide (CoAprovel). The patient should be closely monitored, and the 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 hemodialysis.

Pharmacological Properties

Mode of Action/Pharmacodynamic Characteristics:

Mechanism of action

Irbesartan is a specific insurmountable antagonist of angiotensin II receptors (AT1 subtype). Angiotensin II is an important component of the renin-angiotensin system and is involved in the pathophysiology of hypertension and in sodium homeostasis. Irbesartan does not require metabolic activation for its activity.

Irbesartan blocks the potent vasoconstrictor and aldosterone-secreting effects of angiotensin II by selective antagonism of the angiotensin II (AT1 subtype) receptors localized on vascular smooth muscle cells and in the adrenal cortex. It has no agonist activity at the AT1 receptor and a much greater affinity (more than 8500-fold) for the AT1 receptor than for the AT2 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 AT1 receptors interrupts the feedback loop within the renin-angiotensin system, resulting in increases in plasma renin levels and angiotensin II levels. However, the resultant increase in plasma renin and angiotensin II levels does not overcome the effects of Irbesartan on reducing blood pressure. 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 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. Coadministration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with thiazide diuretics.

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

The combination of Hydrochlorothiazide and Irbesartan produced dose related additive reductions in blood pressure across their therapeutic dose ranges. The addition of 12.5 mg Hydrochlorothiazide to 300 mg Irbesartan once daily in patients not adequately controlled on 300 mg Irbesartan alone resulted in further placebo corrected diastolic blood pressure reductions at trough (24 hours post dosing) of 6.1 mm Hg. The combination of 300 mg Irbesartan and 12.5 mg Hydrochlorothiazide resulted in overall placebo subtracted systolic/diastolic reductions of up to 13.6/11.5 mm Hg. Once daily dosing with 150 mg Irbesartan and 12.5 mg Hydrochlorothiazide showed systolic/diastolic mean placebo-adjusted blood pressure reductions at trough (24 hours post dosing) of 12.9/6.9 mm Hg. Peak effects occurred at 3-6 hours. When assessed by ambulatory blood pressure monitoring, Irbesartan / Hydrochlorothiazide (CoAprovel) 150 / 12.5 mg once daily produced consistent reduction in blood pressure over the 24 hour period with mean 24-hour placebo-subtracted systolic/diastolic reductions of 15.8/10.0 mm Hg. The observed trough-to-peak effects were at least 68% of the corresponding placebo-subtracted peak diastolic and peak systolic responses.

In a clinical trial with patients not adequately controlled on 25 mg Hydrochlorothiazide alone, the addition of Irbesartan to the Hydrochlorothiazide produced mean systolic/diastolic reductions which were 11.1/7.2 mmHg greater than Hydrochlorothiazide alone. Blood pressure was lowered to about the same extent in both standing and supine positions. Orthostatic effects were infrequent, but may be expected to occur in patients who develop intercurrent sodium and/or volume-depletion.

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

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

With Hydrochlorothiazide, onset of diuresis occurred in 2 hours, and peak effect occurred at about 4

hours, while the action persisted for approximately 6-12 hours.

Initial Therapy
Two clinical studies evaluated Irbesartan / Hydrochlorothiazide (CoAprovel) as initial therapy. The first study was conducted in patients with a mean baseline blood pressure of 162/98 mm Hg (Moderate Hypertension) and compared the change from baseline in SeSBP at 8 weeks between the combination group (Irbesartan and HCTZ 150 mg / 12.5 mg) to Irbesartan (150 mg) and to HCTZ (12.5 mg). These initial study regimens were increased at 2 weeks to Irbesartan / Hydrochlorothiazide (CoAprovel) 300 mg / 25 mg, Irbesartan 300 mg, or to HCTZ 25 mg, respectively.

Mean reductions from baseline for SeDBP and SeSBP at trough were 14.6 mmHg and 27.1 mmHg for patients treated with Irbesartan / Hydrochlorothiazide (CoAprovel), 11.6 mm Hg and 22.1 mm Hg for patients treated with Irbesartan, and 7.3 mm Hg and 15.7 mm Hg for patients treated with HCTZ at 8 weeks, respectively. For patients treated with Irbesartan / Hydrochlorothiazide (CoAprovel), the mean change from baseline in SeDBP was 3.0 mm Hg lower (p=0.0013) and the mean change from baseline in SeSBP was 5.0 mm Hg lower (p=0.0016) compared to patients treated with Irbesartan, and 7.4 mm Hg lower (p < 0.0001) and 11.3 mm Hg lower (p < 0.0001) compared to patients treated with HCTZ, respectively.

The second clinical study was conducted in patients with a mean baseline blood pressure of 172/113 mm Hg (Severe Hypertension) and compared trough SeDBP at 5 weeks between the combination group (Irbesartan and HCTZ 150 mg / 12.5 mg) and Irbesartan (150 mg). These initial study regimens were increased at 1 week to Irbesartan/ Hydrochlorothiazide (CoAprovel) 300 mg / 25 mg or to Irbesartan 300 mg, respectively.

At 5 weeks, mean reductions from baseline for SeDBP and SeSBP at trough were 24.0 mm Hg and 30.8 mm Hg for patients treated with Irbesartan / Hydrochlorothiazide (CoAprovel) and 19.3 mm Hg and 21.1 mm Hg for patients treated with Irbesartan, respectively. The mean SeDBP was 4.7 mm Hg lower (p < 0.0001) and the mean SeSBP was 9.7 mmHg lower (p < 0.0001) in the group treated with Irbesartan / Hydrochlorothiazide (CoAprovel) than in the group treated with Irbesartan. Patients treated with Irbesartan / Hydrochlorothiazide (CoAprovel) achieved more rapid blood pressure control with significantly lower SeDBP and SeSBP and greater blood pressure control at every assessment (Week 1, Week 3, Week 5, and Week 7). Maximum effects were seen at Week 7.

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

Non-melanoma skin cancer:
Based on available data from epidemiological studies, cumulative dosedependent association between HCTZ and NMSC has been observed. One study included a population comprised of 71,533 cases of BCC and of 8,629 cases of SCC matched to 1,430,833 and 172,462 population controls, respectively. High HCTZ use (≥ 50,000 mg cumulative) was associated with an adjusted OR of 1.29 (95% CI: 1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for SCC. A clear cumulative dose response relationship was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to HCTZ: 633 cases of lip-cancer were matched with 63,067 population controls, using a risk-set sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR 2.1 (95% CI: 1.7-2.6) increasing to OR 3.9 (3.0-4.9) for high use (~ 25,000 mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose (~ 100,000 mg).

Pharmacokinetics
Concomitant administration of Hydrochlorothiazide and Irbesartan has no effect on the pharmacokinetics of Irbesartan.

Absorption

Irbesartan and Hydrochlorothiazide are orally active agents and do not require biotransformation for their activity. Following oral administration of Irbesartan / Hydrochlorothiazide (CoAprovel), the absolute oral bioavailability is 60-80% and 50-80% for Irbesartan and Hydrochlorothiazide, respectively. Food does not affect the bioavailability of Irbesartan / Hydrochlorothiazide (CoAprovel). Peak plasma concentration occurs at 1.5-2 hours after oral administration for Irbesartan and 1-2.5 hours for Hydrochlorothiazide.

Distribution

Irbesartan is approximately 96% protein-bound in the plasma, and has negligible binding to cellular components of blood. The volume of distribution is 53-93 Liters (0.72-1.24 Liters/Kg). Hydrochlorothiazide is 68% protein-bound in the plasma, and its apparent volume of distribution is 3.6-7.8 Liters/Kg.

Metabolism

In plasma, unchanged Irbesartan accounts for 80-85% of the circulating radioactivity following oral or intravenous administration of 14C Irbesartan. Irbesartan is metabolized by the liver via glucuronide conjugation and oxidation. The major circulating metabolite is Irbesartan glucuronide (~ 6%). Irbesartan undergoes oxidation primarily by the cytochrome P450 isoenzyme CYP2C9; isoenzyme CYP3A4 has negligible effect. It is not metabolized by, nor does it substantially induce or inhibit most isoenzymes commonly associated with drug metabolism (ie, CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2D6, or CYP2E1). Irbesartan does not induce nor inhibit isoenzyme CYP3A4.

Elimination

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 14C Irbesartan is recovered in urine with the remainder in the feces. Less than 2% of the dose is excreted in urine as unchanged Irbesartan. Hydrochlorothiazide is not metabolized and is eliminated by the kidneys. The mean plasma half-life of Hydrochlorothiazide reportedly ranges from 5-15 hours.

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

Special Populations

Gender

In male and female hypertensive subjects, higher (11-44%) plasma concentrations of Irbesartan were observed in females than in males, although, following multiple dosing, males and females did not show differences in either accumulation or elimination half-life. No gender-specific differences in clinical effect have been observed.

Elderly patients

In elderly (male and female) normotensive subjects (65-80 years) with clinically normal renal and hepatic function, the plasma AUC and peak plasma concentrations (C_{max}) of Irbesartan are approximately 20%-50% greater than those observed in younger subjects (18-40 years). Regardless of age, the elimination half-life is comparable. No significant age-related differences in clinical effect have been observed. 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.

Hepatic impairment

In patients with hepatic insufficiency due to mild to moderate cirrhosis, the pharmacokinetics of

Irbesartan are not significantly altered.

Renal impairment
In patients with renal impairment (regardless of degree) and in hemodialysis patients, the pharmacokinetics of Irbesartan are not significantly altered. Irbesartan is not removed by hemodialysis. In patients with severe renal impairment (creatinine clearance < 20 mL/min), the elimination half-life of Hydrochlorothiazide was reported to increase to 21 hours.

Race
In black and white normotensive subjects, the plasma AUC and t½ of Irbesartan are approximately 20-25% greater in blacks than in whites; the peak plasma concentrations (C_{max}) of Irbesartan are essentially equivalent.

Storage
Store at temperatures not exceeding 30°C.

Caution
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

Reporting of Side Effects or any Suspected Adverse Event
For suspected adverse drug reaction, report to the FDA: **www.fda.gov.ph**

Patients should seek medical attention immediately at the first sign of any adverse drug reactions.

You are also encouraged to report any side effects to Sanofi Philippines Pharmacovigilance Unit via email at **PV.Philippines@sanofi.com**. By reporting side effects, you can help provide more information on the safety of this product.

Availability
150 mg / 12.5 mg Film-Coated Tablet: Box of 28's (Blister pack of 14's)
300 mg / 12.5 mg Film-Coated Tablet: Box of 28's (Blister pack of 14's)
300 mg / 25 mg Film-Coated Tablet: Box of 28's (Blister pack of 14's)

Keep out of reach of children.

Manufactured by:
Sanofi Winthrop Industrie
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33565 Carbon Blanc Cedex, France

Imported by:
sanofi-aventis Philippines, Inc.
21st and 22nd Floors, One World Place Corporate Offices,
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Registration Numbers and Date of Last Renewal
150 mg / 12.5 mg Film-Coated Tablet: DRP-001 (05 March 2023)
300 mg / 12.5 mg Film-Coated Tablet: DRP-002 (18 October 2026)
300 mg / 25 mg Film-Coated Tablet : DRP-5717 (12 March 2023)

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