Irbesartan does not require metabolic activation for its activity. Hydrochlorothiazide is a thiazide diuretic. The mechanism of antihypertensive effect of thiazide diuretics is not fully known. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. The diuretic action of hydrochlorothiazide reduces plasma volume, increases plasma renin activity, increases aldosterone secretion, with consequent increases in urinary potassium and bicarbonate loss, and decreases in serum potassium. Presumably through blockade of the renin-angiotensin-aldosterone system, co-administration of irbesartan tends to reverse the potassium loss associated with these diuretics. With hydrochlorothiazide, onset of diuresis occurs in 2 hours, and peak effect occurs at about 4 hours, while the action persists for approximately 6-12 hours.

The combination of hydrochlorothiazide and irbesartan produces 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 placebocorrected diastolic blood pressure reductions at trough (24 hours post-dosing) of 6.1 mmHg. The combination of 300 mg irbesartan and 12.5 mg hydrochlorothiazide resulted in an overall placebo-subtracted systolic/diastolic reductions of up to 13.6/11.5 mmHg. Once daily dosing with 150 mg irbesartan and 12.5 mg hydrochlorothiazide gave systolic/diastolic mean placebo-adjusted blood pressure reductions at trough (24 hours post-dosing) of 12.9/6.9 mmHg in patients with mild-to-moderate hypertension. Peak effects occurred at 3-6 hours. When assessed by ambulatory blood pressure monitoring, the combination 150 mg irbesartan and 12.5 mg hydrochlorothiazide did not improve overall blood pressure control compared to irbesartan monotherapy.

**Composition**

**CoAprovel 150/12.5 mg**
Each tablet contains 150 mg irbesartan and 12.5 mg hydrochlorothiazide.

**CoAprovel 300/12.5 mg**
Each tablet contains 300 mg irbesartan and 12.5 mg hydrochlorothiazide.

Excipients: Microcrystalline cellulose, croscarmellose sodium, lactose monohydrate, magnesium stearate, colloidal hydrated silica, pregelatinised maize starch, red and yellow ferric oxides (E172). The tablets are peach, biconvex, ovalshaped, with a heart debossed on one side and the number 2775 for the 150/12.5 mg and 2776 for the 300/12.5 mg engraved on the other side.

**Properties**

**Pharmacodynamics**

Pharmacotherapeutic group: angiotensin-II antagonists, combinations: ATC code C09DA04.

CoAprovel is a combination of an angiotensin-II receptor antagonist, irbesartan, and a thiazide diuretic, hydrochlorothiazide. The combination of these ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone. Irbesartan is a potent, orally active, selective angiotensin-II receptor (AT1 subtype) antagonist. It is expected to block all actions of angiotensin-II mediated by the AT1 receptor, regardless of the source or route of synthesis of angiotensin-II. The selective antagonism of the angiotensin-II (AT1) receptors results in increases in plasma renin levels and angiotensin-II levels, and a decrease in plasma aldosterone concentration. Serum potassium levels are not significantly affected by irbesartan alone at the recommended doses in patients without risk of electrolyte imbalance. Irbesartan does not inhibit ACE (kininase-II), an enzyme which generates angiotensin-II and also degrades bradykinin into inactive metabolites.
Irbesartan and hydrochlorothiazide are orally active agents and do not require biotransformation for their activity.

Following oral administration of CoAprovel, the absolute oral bioavailability is 60-80% and 50-80% for irbesartan and hydrochlorothiazide, respectively. Food does not affect the bioavailability of CoAprovel. Peak plasma concentration occurs at 1.5-2 hours after oral administration for irbesartan and 1-2.5 hours for hydrochlorothiazide.

Plasma protein binding of irbesartan is approximately 96%, with negligible binding to cellular blood components. The volume of distribution for irbesartan is 53-93 litres. Hydrochlorothiazide is 68% protein-bound in the plasma, and its apparent volume of distribution is 0.83-1.14 l/kg.

Irbesartan exhibits linear and dose proportional pharmacokinetics over the dose range of 10 to 600 mg. A less than proportional increase in oral absorption at doses beyond 600 mg was observed; the mechanism for this is unknown. The total body and renal clearance are 157-176 and 3.0-3.5 ml/min, respectively. The terminal elimination half-life of irbesartan is 11-15 hours. Steady-state plasma concentrations are attained within 3 days after initiation of a once-daily dosing regimen. Limited accumulation of irbesartan (< 20%) is observed in plasma upon repeat- ed once-daily dosing. In a study, somewhat higher plasma concentrations of irbesartan were observed in female hypertensive patients. However, there was no difference in the half-life and accumulation of irbesartan. No dosage adjustment is necessary in female patients. Irbesartan AUC and C_max values were also somewhat greater in elderly subjects (≥ 65 years) than those of young subjects (18-40 years). However the terminal half-life was not significantly altered. No dosage adjustment is necessary in elderly patients.

The blood pressure lowering effect of irbesartan in combination with hydrochlorothiazide is 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. Although not specifically studied with the CoAprovel, rebound hypertension has not been seen with either irbesartan or hydrochlorothiazide.

The effect of the combination of irbesartan and hydrochlorothiazide on morbidity and mortality has not been studied.

Epidemiological studies have shown that long term treatment with hydrochlorothiazide reduces the risk of cardiovascular mortality and morbidity.

There is no difference in response to CoAprovel, regardless of age or gender. When irbesartan is administered concomitantly with a low dose of hydrochlorothiazide (e.g. 12.5 mg daily), the antihypertensive response in black patients approaches that of non-black patients.

**Pharmacokinetics**

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

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Following oral or intravenous administration of 14C irbesartan, 80-85% of the circulating plasma radioactivity is attributable to unchanged irbesartan. Irbesartan is metabolised by the liver via glucuro-
nide conjugation and oxidation. The major circulating metabolite is irbesartan glucuronide (approximately 6%). \textit{In vitro} studies indicate that irbesartan is primarily oxidised by the cytochrome P450 enzyme CYP2C9; isoenzyme CYP3A4 has negligible effect. Irbesartan and its metabolites are eliminated by both biliary and renal pathways. After either oral or I.V. administration of \textsuperscript{14}C irbesartan, about 20% of the radioactivity is recovered in the urine, and the remainder in the faeces. Less than 2% of the dose is excreted in the urine as unchanged irbesartan.

Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidneys. At least 61% of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier, and is excreted in breast milk.

\textit{Renal impairment}: in patients with renal impairment or those undergoing haemodialysis, the pharmacokinetic parameters of irbesartan are not significantly altered. Irbesartan is not removed by haemodialysis. In patients with creatinine clearance < 20 ml/min, the elimination half-life of hydrochlorothiazide was reported to increase to 21 hours.

\textit{Hepatic impairment}: in patients with mild to moderate cirrhosis, the pharmacokinetic parameters of irbesartan are not significantly altered. Studies have not been performed in patients with severe hepatic impairment.

\textbf{Preclinical Safety Data}

\textit{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 drugs 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.

\textit{Irbesartan}: There was no evidence of abnormal sys-
temic or target organ toxicity at clinically relevant doses. In preclinical 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 drug 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.

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.

**Indications**

Treatment of essential hypertension.

This fixed dose combination is indicated in patients whose blood pressure is not adequately controlled on irbesartan or hydrochlorothiazide alone.

**Contraindications**

- Second and third trimester of pregnancy.
- Lactation.
- Hypersensitivity to the active substances, to any of the excipients, or to other sulfonamide-derived substances (hydrochlorothiazide is a sulfonamide derived substance).

The following contraindications are associated with hydrochlorothiazide:
- severe renal impairment (creatinine clearance < 30 ml/min),
- refractory hypokalemia, hypercalcaemia, severe hepatic impairment, biliary cirrhosis and cholestasis.

**Side Effects**

Undesirable effects in patients receiving CoAprovel are generally mild and transient.

In placebo-controlled trials with the combination of irbesartan and hydrochlorothiazide, discontinuation due to any clinical or laboratory adverse event was less frequent for irbesartan/hydrochlorothiazide treated patients than for placebo-treated patients. The incidence of adverse events was not related to gender, age, race, or dose.

Clinical adverse events, probably or possibly related, or of uncertain relationship to therapy occurring with a frequency of 0.5% to < 1% and at a slightly increased incidence in irbesartan/hydrochlorothi-
The following additional adverse events, regardless of whether attributed to therapy, were reported to occur with a frequency of $\geq 1\%$ in clinical trials with irbesartan monotherapy and were not significantly different from placebo: respiratory infection, musculoskeletal pain/myalgia, cough, chest pain, dyspepsia/heartburn, abdominal pain, rash, anxiety/nervousness, UTI.

No clinically significant changes in laboratory test parameters occurred in controlled clinical trials. Although significant increases in plasma creatine kinase occurred more frequently in irbesartan-treated subjects (1.7% vs. 0.7% in placebo-treated subjects), none of these increases were classified as serious, resulted in drug discontinuation, or were associated with identifiable clinical musculoskeletal events.

Hydrochlorothiazide: adverse events (regardless of relationship to drug) reported with the use of hydrochlorothiazide alone include: anorexia, loss of appetite, gastric irritation, diarrhoea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialadenitis, xanthopsia, leucopenia, neutropenia/agranulocytosis, thrombocytopenia, aplastic anaemia, hemolytic anemia, bone marrow depression, photosensitivity reactions, fever, rash, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, urticaria, necrotizing angitis (vasculitis, cutaneous vasculitis), anaphylactic reactions, toxic epidermal necrolysis, respiratory distress (including pneumonitis and pulmonary oedema), hyperglycemia, glycosuria, hyperuricemia, electrolyte imbalance (including hyponatremia and hypokalemia), increases in cholesterol and triglycerides, renal dysfunction, interstitial nephritis, muscle spasm, weakness, restlessness, transient blurred vision, light-headedness, postural hypotension, vertigo, paraesthesia, cardiac arrhythmias, sleep disturbances, depression.

**Warnings and Precautions**

**Hypotension- Volume-depleted patients:** CoAprovel has been rarely associated with symptomatic hypotension in hypertensive patients without other risk factors.
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 CoAprovel. 

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 CoAprovel, a similar effect should be anticipated. 

Renal impairment and kidney transplantation: when CoAprovel 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 CoAprovel in patients with a recent kidney transplantation. CoAprovel should not be used in patients with severe renal impairment (creatinine clearance < 30 ml/min). Thiazide diuretic-associated azotemia 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 CoAprovel in patients with hepatic impairment. 

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

Primary aldosteronism: patients with primary aldosteronism generally will not respond to anti-hypertensive drugs acting through inhibition of the renin-angiotensin system. Therefore, the use of CoAprovel is not recommended. 

Metabolic and endocrine effects: thiazide therapy may impair glucose tolerance. In diabetic patients dosage adjustments of insulin or oral hypoglycemic 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 mg dose contained in CoAprovel, minimal or no effects were reported. 

Hyperuricemia 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 (hypokalemia, hypotension, and hypochloremic 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 hypokalemia may develop with the use of thiazide diuretics, concurrent therapy with irbesartan may reduce diuretic-induced hypokalemia. The risk of hypokalemia is greatest in patients with cirrhosis of the liver, 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 CoAprovel hyperkalemia might occur, especially in the presence of renal impairment and/or heart failure, and diabetes mellitus. Adequate monitoring of serum potassium in patients at risk is recommended. Potassium-sparing diuretics, potassium supplements or potassium-containing salts substitutes should be coadministered cautiously with CoAprovel.
There is no evidence that irbesartan would reduce or prevent diuretic-induced hyponatremia. 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.

Anti-doping test: hydrochlorothiazide containing this medication 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-angiotensinaldosterone 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 hypertension, azotemia, oliguria, or rarely acute renal failure. As with any anti-hypertensive 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.

In the first trimester of pregnancy, CoAprovel is not recommended.

Pregnancy and Lactation
Pregnancy: thiazides cross the placental barrier and appear in cord blood. They may cause decrease placental perfusion, foetal electrolyte disturbances and possibly other reactions that have occurred in the adults. Cases of neonatal thrombocytopenia, or foetal or neonatal jaundice have been reported with maternal thiazide therapy. Since CoAprovel contains hydrochlorothiazide, it is not recommended during the first trimester of pregnancy.

A switch to a suitable alternative treatment should be carried out in advance of a planned pregnancy.

In the second and third trimesters, substances that act directly on the reninangiotensin-system can cause foetal or neonatal renal failure, foetal skull hypoplasia and even foetal death, therefore, CoAprovel is contraindicated in the second and third trimesters of pregnancy.

If pregnancy is diagnosed, CoAprovel should be discontinued as soon as possible, skull and renal function should be checked with echography if, inadvertently, the treatment was taken for a long period.

Lactation: because of the potential adverse effects on the nursing infant, CoAprovel is contraindicated during lactation. It is not known if irbesartan is excreted in human milk. It is excreted in the milk of lactating rats. Thiazides appear in human milk and may inhibit lactation.

Effects on Ability to Drive and Operate Machinery
The effect of CoAprovel on ability to drive and use machines has not been studied, but based on its pharmacodynamic properties, CoAprovel is unlikely to affect this ability. When driving vehicles or operating machines, it should be taken into account that occasionally dizziness or weariness may occur during treatment of hypertension.

Overdosage
No specific information is available on the treatment of overdosage with CoAprovel. 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 and/or gastric lavage. Activated char-
coal may be useful in the treatment of overdose. 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. Overdosage with hydrochlorothiazide is associated with electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. The most common signs and symptoms of overdosage are nausea and somnolence. Hypokalemia may result in muscle spasms and/or accentuate cardiac arrhythmias associated with the concomitant use of digitalis glycosides or certain anti-arrhythmic drugs. Irbesartan is not removed by haemodialysis. The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

**Shelf Life**

2 years.

**Special Precautions for Storage**

Do not store above 30°C. Store in the original package.

**Drug Interactions**

*Other antihypertensive agents:* the antihypertensive effect of CoAprovel may be increased with the concomitant use of other antihypertensive agents. Irbesartan and hydrochlorothiazide (at doses up to 300 mg irbesartan/25 mg hydrochlorothiazide) have been safely administered with other antihypertensive agents 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. 

*Lithium:* reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors. Furthermore, renal clearance of lithium is reduced by thiazides so the risk of lithium toxicity could be increased with CoAprovel. Lithium and CoAprovel should be co-administered with caution and careful monitoring of serum lithium levels is recommended.

*Medicinal products 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 drugs associated with potassium loss and hypokalemia (e.g. other kaliuretic diuretics, laxatives, amphotericin, carbenoxolone, penicillin G sodium, salicylic acid derivatives). Conversely, based on the experience with the use of other drugs that blunt the renin-angiotensin system, concomitant use of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other drugs that may increase serum potassium levels (e.g. heparin sodium) may lead to increases in serum potassium.

*Medicinal products affected by serum potassium disturbances:* periodic monitoring of serum potassium is recommended when CoAprovel is administered with drugs affected by serum potassium disturbances (e.g. digitalis glycosides, antiarrhythmics). Additional information on irbesartan interactions: the pharmacokinetics of digoxin were not altered by co-administration of a 150 mg dose of irbesartan in healthy male volunteers. The pharmacokinetics of irbesartan are not affected by coadministration of hydrochlorothiazide. Irbesartan is mainly metabolised by CYP2C9 and to a lesser extent by glucuronidation. Inhibition of the glucuronyl transferase pathway is unlikely to result in clinically significant interactions. In vitro interactions were observed between irbesartan and warfarin, tolbutamide (CYP2C9 substrates) and nifedipine (CYP2C9 inhibitor). However, no significant pharmacokinetic or pharmacodynamic interactions were observed when irbesartan was co-administered with warfarin in healthy male volunteers. The pharmacokinetics of irbesartan are
not affected by co-administration of nifedipine. The effects of CYP2C9 inducers such as rifampicin on the pharmacokinetics of irbesartan were not evaluated. Based on in vitro data, no interaction would be expected to occur with drugs whose metabolism is dependent upon cytochrome P450 isoenzymes CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2D6, CYP2E1 or CYP3A4. Additional information on hydrochlorothiazide interactions: when administered concurrently, the following drugs may interact with thiazide diuretics:

- **Alcohol, Barbiturates, or Narcotics:** potentiation of orthostatic hypotension may occur;
- **Antidiabetic drugs (oral agents and insulins):** dosage adjustment of the antidiabetic drug may be required;
- **Cholestyramine and Colestipol resins:** absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins;
- **Corticosteroids, ACTH:** electrolyte depletion, particularly hypokalemia, may be increased;
- **Digitalis glycosides:** thiazide induced hypokalemia or hypomagnesaemia favour the onset of digitalis-induced cardiac arrhythmias;
- **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 medication:** dosage adjustments of antigout medications 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 drugs (e.g. Vitamin D therapy) must be prescribed, serum calcium levels should be monitored and calcium dosage adjusted accordingly;
- **Other interactions:** the hyperglycaemic effect of beta-blockers and diazoxide may be enhanced by thiazides. Anticholinergic agents (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 drugs (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.

**Dosage and Administration**

CoAprovel can be used once daily, with or without food in patients whose blood pressure is not adequately controlled by irbesartan or hydrochlorothiazide alone.

Dose titration with the individual components (i.e. irbesartan and hydrochlorothiazide) can be recommended.

When clinically appropriate direct change from monotherapy to the fixed combinations may be considered:

- CoAprovel 150/12.5 mg may be administered in patients whose blood pressure is not adequately controlled by hydrochlorothiazide or irbesartan 150 mg alone;
- CoAprovel 300/12.5 mg may be administered in patients insufficiently controlled by irbesartan 300 mg or by CoAprovel 150/12.5 mg.

Doses higher than 300 mg irbesartan/25 mg hydrochlorothiazide once daily are not recommended. When necessary, CoAprovel may be administered with another antihypertensive drug.

**Renal impairment:** due to the hydrochlorothiazide component, CoAprovel is not recommended for patients with severe renal dysfunction (creatinine
clearance < 30 ml/min). Loop diuretics are preferred to thiazides in this population. No dosage adjustment is necessary in patients with renal impairment whose renal creatinine clearance is ≥ 30 ml/min. 

*Intravascular Volume Depletion:* Volume and/or sodium depletion should be corrected prior to administration of CoAprovel. 

*Hepatic Impairment:* CoAprovel is not indicated in patients with severe hepatic impairment. Thiazides should be used with caution in patients with impaired hepatic function. No dosage adjustment of CoAprovel is necessary in patients with mild to moderate hepatic impairment. 

*Elderly patients:* no dosage adjustment of CoAprovel is necessary in elderly patients. 

*Children:* safety and efficacy of CoAprovel have not been established in children (<18 years). 

**Packaging**

t: 28, 56 in PVC/PVDC/aluminium blisters.