SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Converium 150mg tablets
Converium 300mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Converium tablets 150mg: each tablet contains 150mg irbesartan
Converium tablets 300mg: each tablet contains 300mg irbesartan
Excipients:
31.0mg of lactose monohydrate per Converium 150mg tablet
62.0mg of lactose monohydrate per Converium 300mg tablet
For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablet
Converium tablets 150mg: White, round flat, scored tablets having a diameter of 10.5mm
Converium tablets 300mg: White, round flat, scored tablets having a diameter of 12.7mm
Converium 150mg and 300mg tablets can be divided into equal halves

4. CLINICAL PARTICULARS

4.1 Therapeutic Indication

Treatment of essential hypertension.
Treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria (>300 mg/day) in patients with type 2 diabetes and hypertension. In this population, Converium reduces the rate of progression of nephropathy as measured by the occurrence of doubling of serum creatinine or end- stage renal disease (need for dialysis or renal transplantation).

4.2 Posology and method of administration

The usual recommended initial and maintenance dose is 150mg once daily, with or without food. Converium at a dose of 150 mg once daily generally provides a better 24 hour blood pressure control than 75 mg. However, initiation of therapy with 75 mg could be considered, particularly in haemodialysed patients and in the elderly over 75 years.

In patients insufficiently controlled with 150 mg once daily, the dose of Converium can be increased to 300 mg, or other anti-hypertensive agents can be added. In particular, the addition of a diuretic such as hydrochlorothiazide has been shown to have an additive effect with Converium (see section 4.5).

In hypertensive type 2 diabetic patients therapy should be initiated at 150mg irbesartan once daily and titrated up to 300mg once daily as the preferred maintenance dose for treatment of renal disease. The demonstration of renal benefit of Converium in hypertensive type 2 diabetic patients is based on studies where irbesartan was used in addition to other antihypertensive agents, as needed, to reach target blood pressure.

Renal impairment: no dosage adjustment is necessary in patients with impaired renal function. A lower starting dose (75 mg) should be considered for patients undergoing hemodialysis. (see section 4.4)

Hepatic impairment: no dosage adjustment is necessary in patients with mild to moderate hepatic impairment. There is no clinical experience in patients with severe hepatic impairment.

Elderly patients*:* although consideration should be given to initiating therapy with 75 mg in patients over 75 years of age, dosage adjustment is not usually necessary for the elderly.

Pediatric patients: irbesartan is not recommended for use in children and adolescents due to insufficient data on safety and efficacy (see sections 4.7, 5.1 and 5.2).

4.3 Contraindications

- Hypersensitivity to irbesartan or to any of the excipients. (see section 6.1).
- Second and third trimester of pregnancy (see sections 4.4 and 4.6).

4.4 Special Warnings and Precautions for Use

Intravascular volume depletion*:* symptomatic hypotension, especially after the first dose, may 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 the administration of Converium.

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 kidneyare treated with medicinal products that affect the renin-angiotensin-aldosterone system. While this is not documented with Converium, a similar effect should be anticipated with angiotensin-II receptor antagonists.

Renal impairment and kidney transplantation: when Converium is used in patients with impaired renal function, a periodic monitoring of potassium and creatinine serum levels is recommended. There is no experience regarding the administration of Converium in patients with a recent kidney transplantation.

Hypertensive patients with type 2 diabetes and renal disease*:* the effects of irbesartan both on renal and cardiovascular events were not uniform across all subgroups, in an analysis carried out in the studywith patients with advanced renal disease. In particular, they appeared less favourable in women and non-white subjects (see section 5.1).

Hyperkalemia*:* as with other medicinal products that affect the renin-angiotensin-aldosterone system, hyperkalemia may occur during the treatment with Converium, especially in the presence of renal impairment, overt proteinuria due to diabetic renal disease, and/or heart failure. Close monitoring of serum potassium in patients at risk is recommended (see section 4.5).

Lithium*:* the combination of lithium and Converium is not recommended (see section 4.5).

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

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

General*:* in patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with angiotensin converting enzyme inhibitors or angiotensin-II receptor antagonists that affect this system has been associated with acute hypotension, azotaemia, oliguria, or rarely acute renal failure. As with any antihypertensive

agent, excessive blood pressure decrease in patients with ischaemic cardiopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke.
As observed for angiotensin converting enzyme inhibitors, irbesartan and the other angiotensin antagonists are apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population (see section 5.1).

Pregnancy: Angiotensin-II receptor antagonist (AIIRAs) should not be initiated during pregnancy. Unless continued AIIRAs therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6)

Lactose: this medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Paediatric patients: irbesartan has been studied in paediatric populations aged 6 to 16 years old but the current data are insufficient to support an extension of the use in children until further data become available (see sections 4.7, 5.1 and 5.2).

Effects on ability to drive and use machines: No studies on the effects on the ability to drive and use machines have been performed. CONVERIUM is unlikely to affect your ability to drive or use machines. However, occasionally dizziness or weariness may occur during treatment of high blood pressure.

4.5 Interactions with other medicinal products and other forms of interaction

Diuretics and other antihypertensive agents*:* other antihypertensive agents may increase the hypotensive effects of irbesartan; however Converium has been safely administered with other antihypertensive agents, such as beta-blockers, long-acting calcium channel blockers, and thiazide diuretics. Prior treatment with high dose diuretics may result in volume depletion and a risk of hypotension when initiating therapy with Converium (see section 4.4).

Potassium supplements and potassium-sparing diuretics*:* based on experience with the use of other medicinal products 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 serum potassium levels (e.g. heparin) may lead to increases in serum potassium and is, therefore, not recommended (see section 4.4).

Lithium*:* reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors. Similar effects have been very rarely reported with irbesartan so far. Therefore, this combination is not recommended (see section 4.4). If the combination proves necessary, careful monitoring of serum lithium levels is recommended.

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

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

4.6 Pregnancy and Lactation

Pregnancy:

The use of AIIRAs is not recommended during the first trimester of pregnancy (see section 4.4). The use of AIIRAs is contraindicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitorsduring the first trimester of pregnancy has not been conclusive; however a small increase in risk cannotbe excluded. Whilst there is no controlled epidemiological data on the risk with Angiotensin II Receptor Antagonists (AIIRAs), similar risks may exist for this class of drugs. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to AIIRAs therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (see section 5.3).
Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.
Infants whose mothers have taken AIIRAs should be closely observed for hypotension (see also sections 4.3 and 4.4).

Lactation*:* Because no information is available regarding the use of Converium during breast-feeding, Converium is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

4.7 Undesirable 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). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Investigations:
Very common: Hyperkalaemia
Common: Significant increases in plasma creatine kinase

Cardiac disorders:
Uncommon: tachycardia

Nervous system disorders:
Common: dizziness, orthostatic dizziness

Respiratory, thoracic and mediastinal disorders:
Uncommon: cough

Gastrointestinal disorders:
Common: nausea/vomiting
Uncommon: diarrhoea, dyspepsia/heartburn

Musculoskeletal and connective tissue disorders:
Common: musculoskeletal pain

Vascular disorders:
Common: orthostatic hypotension
Uncommon: flushing

General disorders and administration site conditions:
Common: fatigue
Uncommon: chest pain

Reproductive system and breast disorders:
Uncommon: sexual dysfunction

The following additional adverse reactions have been reported during post–marketing experience; they are derived from spontaneous reports and therefore, the frequency of these adverse reactions is not known:

Nervous system disorders: Headache

Ear and labyrinth disorders: Tinnitus

Gastrointestinal disorders: Dysgeusia

Renal and urinary disorders: Impaired renal function including cases of renal failure in patients at risk (see section 4.4)

Skin and subcutaneous tissue disorders: Leukocytoclastic vasculitis

Musculoskeletal and connective tissue disorders: Arthralgia, myalgia (in some cases associated with increased plasma creatine kinase levels), muscle cramps

Metabolism and nutrition disorders: Hyperkalaemia

Immune system disorders: Hypersensitivity reactions such as angioedema, rash, urticaria

Hepato-biliary disorders: Hepatitis, abnormal liver function

4.8 Overdose

Experience in adults exposed to doses of up to 900 mg/day for 8 weeks revealed no toxicity. The most likely manifestations of overdose are expected to be hypotension and tachycardia; bradycardia might also occur from overdose. No specific information is available on the treatment of overdose with

Converium. The patient should be closely monitored, and the treatment should be symptomatic and supportive. Suggested measures include induction of emesis and/or gastric lavage. Activated charcoal may be useful in the treatment of overdose. Irbesartan is not removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmaco-therapeutic group: angiotensin II antagonists, plain.
ATC code C09C A04.
Mechanism of action: irbesartan is a potent, orally active, selective angiotensin-II receptor (type AT_1) antagonist. Irbesartan is expected to block all actions of angiotensin-II mediated by the AT_1 receptor, regardless of the source or route of synthesis of angiotensin-II. The selective antagonism of the angiotensin-II (AT_1) 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. Irbesartan does not inhibit ACE (kininase-II), an enzyme which generates angiotensin-II and also degrades bradykinin into inactive metabolites. Irbesartan does not require metabolic activation for its activity.

5.2 Pharmacokinetic Properties

After oral administration, irbesartan is well absorbed. Concomitant food intake does not significantly influence the bioavailability of irbesartan. Plasma protein binding is approximately 96%, with negligible binding to cellular blood components. The volume of distribution is 53-93 litres. Following oral or intravenous administration of ^{14}C irbesartan, 80-85% of the circulating plasma radioactivity is attributable to unchanged irbesartan. Irbesartan is metabolised by the liver via glucuronide conjugation and oxidation. The major circulating metabolite is irbesartan glucuronide (approximately 6%).
Irbesartan 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 (twice the maximal recommended dose) was observed; the mechanism for this is unknown. Peak plasma concentrations are attained at 1.5-2 hours after oral administration. The total body and renal clearance are 157-176 and 3-3.5 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 repeated once-daily dosing.
Irbesartan and its metabolites are eliminated by both biliary and renal pathways. After either oral or IV administration of ^{14}C irbesartan, about 20% of the radioactivity is recovered in the urine, and the remainder in the faeces. Less than 2% of the dose is excreted in the urine as unchanged irbesartan.
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.
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 severehepatic impairment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Converium 150mg and 300mg tablets also contain:
Lactose monohydrate
Pregelatinised Starch
Croscarmellose Sodium
Colloidal Anhydrous Silica
Poloxamer 188
Microcrystalline Cellulose

Magnesium Stearate

6.2 Shelf Life

24 months

6.3 Special Precautions for Storage

Store below 30^{o}C

6.4 Nature and Contents of Container

The tablets are folded into PVC/PVDC/aluminium foil blisters.
Available pack sizes are: 14 tablets; 28 tablets; 30 tablets; 60 tablets and 100 tablets

6.5 MANUFACTURER

Medochemie (Far East) Ltd. (Oral Facility), No. 40 Street 6 Vietnam Singapore Industrial Park II, Binh Duong Industry Service Urban Complex, Hoa Phu ward, Thu Dau Mot city, Vietnam

6.6 PRODUCT REGISTRATION HOLDER

Komedic Sdn Bhd, No. 4, Jalan PJS 11/14, Bandar Sunway 46150 Petaling Jaya, Selangor

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