SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

IROVEL 150/300 TABLET

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

IROVEL 150 TABLET

Each tablet contains
Irbesartan USP….....150 mg
Lactose monohydrate NF……95mg

IROVEL 300 TABLET

Each tablet contains
Irbesartan USP .....300 mg
Lactose monohydrate NF……250mg

The product contains lactose.

For the full list of excipients, **see section 6.1.**

3. PHARMACEUTICAL FORM

Dosage Form: Tablet

Physical description:

Irovel 150: A flat beveled edge, white, circular uncoated tablet having a break line on one side and plain on the other side.

Irovel 300: A white caplet shape uncoated tablets having a break line on one side and plain on the other side.

“The breakline is not intended for division of the tablet. The tablet should beswallowed as a whole"

Prescription Only Medicine (POM)

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

IROVEL TABLET is indicated in adults for the treatment of essential hypertension.

It is also indicated for the treatment of renal disease in adult patients with hypertension and type 2 diabetes mellitus as part of an antihypertensive medicinal product regimen.

4.2. Posology and method of administration

IROVEL TABLET is not suitable for dosages below 150 mg, therefore other suitable available strengths and dosage forms of irbesartan should be used in such cases.

Posology

The usual recommended initial and maintenance dose is 150 mg once daily, with or without food. Irbesartan 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 irbesartan can be increased to 300 mg, or other antihypertensive agents can be added. In particular, the addition of a diuretic such as hydrochlorothiazide has been reported to have an additive effect with irbesartan.

In hypertensive type 2 diabetic patients, therapy should be initiated at irbesartan 150 mg once daily and titrated up to 300 mg once daily as the preferred maintenance dose for treatment of renal disease.

The demonstration of renal benefit of irbesartan in hypertensive type 2 diabetic patients is based on reported studies where irbesartan was used in addition to other antihypertensive agents, as needed, to reach target blood pressure.

Special populations

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 haemodialysis.

Hepatic impairment

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

Older people

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 older people.

Paediatric population

The safety and efficacy of irbesartan in children aged 0 to 18 years has not been reported. Currently available data are described in section side effects, pharmacodynamics properties and pharmacokinetics properties but no recommendation on a posology can be made.

Method of Administration

For oral use.

4.3. Contraindications

- Hypersensitivity to the irbesartan or to any of the excipients of this product (listed in section 6.1).
- Second and third trimesters of pregnancy.
- The concomitant use of irbesartan with aliskiren-containing products is contraindicated inpatients with diabetes mellitus or renal impairment [glomerular filtration rate (GFR) <60 ml/min/1.73m^2].

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 irbesartan.

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 medicinal products that affect the renin-angiotensin-aldosterone system.

While this is not documented with irbesartan, a similar effect should be anticipated with angiotensin-II receptor antagonists.

Renal impairment and kidney transplantation

When irbesartan is used in patients with impaired renal function, a periodic monitoring of potassium and creatinine serum levels is recommended. There is no experience reported regarding the administration of irbesartan in patients with a recent kidney transplantation.

Hypertensive patients with type 2 diabetes and renal disease

In a reported analysis in patients with advanced renal disease, the effects of irbesartan both on renal and cardiovascular events were reported to be not uniform across all subgroups. In particular, they appeared to be less favorable in women and non-white subjects.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

There is reported evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended. If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Hyperkalemia

As with other medicinal products that affect the renin-angiotensin-aldosterone system, hyperkalemia may occur during the treatment with irbesartan, 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.

Lithium

The combination of lithium and irbesartan 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 irbesartan 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 reported 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 inthe black hypertensive population.

Pregnancy

Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAsshould be stopped immediately, and, if appropriate, alternative therapy should be started.

Paediatric population

Irbesartan has been reported to be studied in paediatric populations aged 6 to 16 years old but the reported data was insufficient to support an extension of the use in children until further information becomes available.

Excipients

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

4.5. Interaction with other medicinal products and other forms of interaction

Diuretics and other antihypertensive agents

Other antihypertensive agents may increase the hypotensive effects of irbesartan; however, irbesartan 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 irbesartan.

Aliskiren-containing products and ACE-inhibitors

Reported clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent.

Potassium supplements and potassium-sparing diuretics

Based on reported 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.

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. 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 (NSAIDs) [i.e. selective COX-2 inhibitors, acetylsalicylic acid (> 3 g/day) and non-selective NSAIDs], attenuation of the antihypertensive effect may occur.

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

Additional information on irbesartan interactions

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

4.6. Fertility, 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 trimesters of pregnancy(see sections 4.3 and 4.4).

Epidemiological evidence reported regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however, a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data reported on the risk with 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 antihypertensive 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 AIIRA therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia).

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.

Breast-feeding

Since no information is available regarding the use of irbesartan during breast-feeding, irbesartan is not recommended and alternative treatments with better established safety

profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.
It is unknown whether irbesartan or its metabolites are excreted in human milk. Reported pharmacodynamic/toxicological data in rats have shown excretion of irbesartan or its metabolites in milk.

Fertility

Irbesartan had no reported effect upon fertility of treated rats and their offspring up to the dose levels inducing the first signs of parental toxicity.

4.7. Effects on ability to drive and use machines

Based on its pharmacodynamic properties, irbesartan is unlikely to affect the ability to drive and use machines. When driving vehicles or operating machines, it should be taken into account that dizziness or weariness may occur during treatment.

4.8. Undesirable effects

In reported placebo-controlled trials in patients with hypertension, the overall incidence of adverse events did not differ between the irbesartan (56.2%) and the placebo groups (56.5%). Discontinuation due to any clinical or laboratory adverse event was less frequent for irbesartan-treated patients (3.3%) than for placebo-treated patients (4.5%). The incidence of adverse events was not related to dose (in the recommended doserange), gender, age, race, or duration of treatment.

In diabetic hypertensive patients with microalbuminuria and normal renal function, orthostatic dizziness and orthostatic hypotension were reported in 0.5% of the patients (i.e., uncommon).

The frequency of reported adverse reactions listed below in table and are 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.

The following table presents the adverse drug reactions that were reported in placebo-controlled studies in which hypertensive patients received irbesartan. Terms marked with a star (*) refer to the adverse reactions that were additionally reported in > 2% of diabetic hypertensive patients with chronic renal insufficiency and overt proteinuria and in excess

of placebo. Adverse reactions additionally reported from post marketing experience arealso listed.

Blood and lymphatic system disorders	
Not known:	Thrombocytopenia
Immune system disorders:	
Not known:	Hypersensitivity reactions such as angioedema, rash, urticaria, anaphylactic reaction, anaphylactic shock
Metabolism and nutrition disorders:	
Not known:	Hyperkalemia
Nervous system disorders:	
Common:	Dizziness, orthostatic dizziness*
Not known:	vertigo, headache
Ear and labyrinth disorder:	
Not known:	Tinnitus
Cardiac disorders:	
Uncommon:	Tachycardia
Vascular disorders:	
Common:	Orthostatic hypotension*
Uncommon:	Flushing
Respiratory, thoracic and mediastinal disorders:	
Uncommon:	Cough
Gastrointestinal disorders:	
Common:	Nausea/vomiting
Uncommon:	Diarrhoea, dyspepsia/heartburn
Not known:	Dysgeusia
Hepatobiliary disorders:	
Uncommon:	Jaundice
Not known:	Hepatitis, abnormal liver function
Skin and subcutaneous tissue disorders:	
Not known:	Leukocytoclastic vasculitis
Musculoskeletal and connective tissue disorders:	
Common:	Musculoskeletal pain*

Not known:	Arthralgia, myalgia (in some cases associated with increased plasmacreatine kinase levels), muscle cramps
Renal and urinary disorders:	
Not known:	Impaired renal function including cases of renal failure in patients atrisk
Reproductive system and breast disorders:	
Uncommon:	Sexual dysfunction
General disorders and administration site conditions:	
Common:	Fatigue
Uncommon:	Chest pain
Investigations:	
Very common:	Hyperkalaemia* was reported more often in diabetic patients treated with irbesartan than with placebo. In diabetic hypertensive patients with microalbuminuria and normal renal function, hyperkalaemia (≥ 5.5 mEq/L) reported in 29.4% of the patients in the irbesartan 300 mg group and 22% of the patients in the placebo group. In diabetic hypertensive patients with chronic renal insufficiency and overt proteinuria, hyperkalaemia (≥ 5.5 mEq/L) was reported in 46.3% of the patients in the irbesartan group and 26.3% of the patients in the placebo group.
Common:	Significant increases in plasma creatine kinase (1.7%) were commonly reported in irbesartan treated subjects. None of these increases were associated with identifiable clinical musculoskeletal events. In 1.7% of hypertensive patients with advanced diabetic renal disease treated with irbesartan, a decrease in haemoglobin*, which was not clinically significant, has been reported.

Paediatric population

In a reported randomised study involving hypertensive children and adolescents aged 6 to 16 years, the following adverse reactions were reported: headache (7.9%), hypotension (2.2%), dizziness (1.9%) and cough (0.9%). In the reported 26 week study the most frequent laboratory abnormalities reported were creatinine increases (6.5%) and elevated creatinine kinase (CK) values in 2% of child recipients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to **TMDA.**

4.9. Overdose

Based on experience in adults exposed to doses of up to 900 mg/day for 8 weeks, no toxicity has been reported. 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 irbesartan. 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

Pharmacotherapeutic 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. It 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

Absorption

After oral administration, irbesartan is well absorbed with absolute bioavailability values of approximately 60-80%. Concomitant food intake does not significantly influence the bioavailability of irbesartan.

Distribution

Plasma protein binding is reported as approximately 96%, with negligible binding to cellular blood components. The volume of distribution is reported as 53 - 93 litres.

Biotransformation

Following oral or intravenous administration of ^{14}C irbesartan, 80 - 85% of the circulating plasma radioactivity is attributable to unchanged irbesartan. Irbesartan is reported to be metabolised by the liver via glucuronide conjugation and oxidation. The major circulating metabolite has been reported to be irbesartan glucuronide (approximately 6%). Reported *in vitro* studies indicate that irbesartan is primarily oxidised by the cytochrome P450 enzyme CYP2C9; isoenzyme CYP3A4 has negligible

effect.

Linearity/non-linearity

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) has been reported, however 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 reported as 157 - 176 and 3 - 3.5 ml/min, respectively. The terminal elimination half-life of irbesartan is reported as 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 reported in plasma upon repeated once-daily dosing. In a reported study, somewhat higher plasma concentrations of irbesartan were reported 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 older 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 older people.

Elimination

Irbesartan and its metabolites are reported to be eliminated by both biliary and renal pathways. After either oral or IV administration of ^{14}C irbesartan, about 20% of the radioactivity is reported to be recovered in the urine, and the remainder in the faeces.Less than 2% of the dose is excreted in the urine as unchanged irbesartan.

Paediatric population

The pharmacokinetics of irbesartan has been reported in hypertensive children after the administration of single and multiple daily doses of irbesartan (2 mg/kg) up to a maximum daily dose of 150 mg for four weeks. Results reported from the study showed that C_{max}, AUC and clearance rates were comparable to those reported in adult patients receiving 150 mg irbesartan daily. A limited accumulation of irbesartan (18%) in plasma was reported upon repeated once daily dosing.

Renal impairment

In patients with renal impairment or those undergoing haemodialysis, the pharmacokinetic parameters of irbesartan are not reported to be significantly altered. Irbesartan is not removed by haemodialysis.

Hepatic impairment

In patients with mild to moderate cirrhosis, the pharmacokinetic parameters of irbesartan are not reported to be significantly altered. No studies have been reported in patients withsevere hepatic impairment.

5.3. Preclinical safety data

There was no reported evidence of abnormal systemic or target organ toxicity at clinically relevant doses. In reported non-clinical safety studies, high doses of irbesartan (≥ 250 mg/kg/day in rats and ≥ 100 mg/kg/day in macaques) caused a reduction of red

blood cell parameters (erythrocytes, haemoglobin, haematocrit).

At very high doses (≥ 500 mg/kg/day) degenerative changes in the kidney (such as interstitial nephritis, tubular distension, basophilic tubules, increased plasma concentrations of urea and creatinine) were reported to be induced by irbesartan in the rat and the macaque and are considered secondary to the hypotensive effects of the medicinal product which led to decreased renal perfusion. Furthermore, it has been reported that 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 reported evidence of mutagenicity, clastogenicity or carcinogenicity.

Fertility and reproductive performance were not affected in reported studies of male and female rats even at oral doses of irbesartan causing some parental toxicity (from 50 to 650 mg/kg/day), including mortality at the highest dose. No significant effects on the number of corpora lutea, implants, or live foetuses were reported. Irbesartan did notaffect survival, development, or reproduction of offspring. Reported studies in animals indicated that the radiolabelled irbesartan is detected in rat and rabbit foetuses. Irbesartan is reported to be excreted in the milk of lactating rats.

Animal studies with irbesartan reported 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 were reported at doses causing

significant maternal toxicity, including mortality. No teratogenic effects were reported in the rat or rabbit.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose monohydrate, Microcrystalline cellulose, Croscarmellose sodium, Maize starch, Colloidal Anhydrous Silica, Pregelatinised Starch, Poloxamer NF (188), Talc, Magnesium Stearate

6.2. Incompatibilities

Not Applicable

6.3. Shelf life

36 Months

6.4. Special precautions for storage

Do not store above 30°C. Protect from light.

6.5. Nature and contents of container

IROVEL TABLETS are available in Alu-Alu Strip pack of 10's tablets. Each 3 strips packed in a duly overprinted show box along with package insert.

6.6. Instructions for use and handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Sun Pharmaceutical Industries
limited,Sun House, Plot No. 201 B/1,
Western Express Highway, Goregoan
(E),Mumbai, Maharashtra

Manufacturer

Sun Pharma Laboratories Limited,
6-9, EPIP, Kartholi, Bari Brahmana,
Jammu-181133,
Jammu & Kashmir, India

8. MARKETING AUTHORISATION NUMBER

TAN 22 HM 0488

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

05th December, 2022

10. DATE OF REVISION OF THE TEXT