SCHEDULING STATUS:

S3

PROPRIETARY NAME AND DOSAGE FORM:

APROVEL® 75 mg tablets

APROVEL® 150 mg tablets

APROVEL® 300 mg tablets

COMPOSITION:

APROVEL tablets contain 75 mg, 150 mg or 300 mg of irbesartan.

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

Contains lactose monohydrate.

PHARMACOLOGICAL CLASSIFICATION:

A 7.1.3 Other hypotensives

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Mechanism of Action:

Irbesartan is a specific antagonist of angiotensin II receptors (AT_1 subtype), known as an angiotensin receptor blocker (ARB). Angiotensin II is an important component of the renin-angiotensin system (RAS) and is involved in the pathophysiology of hypertension and in sodium homeostasis.

Irbesartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selective antagonism of the angiotensin II (AT_1 subtype) receptors localised on vascular smooth muscle cells and in the adrenal cortex.

It has no agonist activity at the AT_1 receptor and a much greater affinity (more than 8500-fold) for

the AT_1 receptor than for the AT_2 receptor (a receptor that has not been shown to be associated with cardiovascular homeostasis).

Irbesartan does not inhibit enzymes involved in the renin-angiotensin system (i.e. renin, angiotensin converting enzyme [ACE]), or affect other hormone receptors or ion channels involved in the cardiovascular regulation of blood pressure and sodium homeostasis.
Irbesartan blockade of AT_1 receptors interrupts the feedback loop within the renin-angiotensin system, resulting in increases in plasma renin levels and angiotensin II levels.
Aldosterone plasma concentrations decline following irbesartan administration. However, serum potassium levels are not significantly affected (mean increase of < 0,1 mmol/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.

Pharmacokinetic Properties:
Irbesartan is an orally active agent and does not require biotransformation for its activity.
Following oral administration, irbesartan is well absorbed. The absolute oral bioavailability of irbesartan is 60-80 %. Food does not affect the bioavailability. Peak plasma concentration occurs at 1,5-2 hours after oral administration.

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 litres.

In plasma, unchanged irbesartan accounts for 80-85 % of the circulating radioactivity following oral or intravenous administration of 14C irbesartan.

Irbesartan is metabolised by the liver via glucuronide conjugation and oxidation. The major circulating metabolite is irbesartan glucuronide (≈ 6 %). Irbesartan undergoes oxidation primarily by the cytochrome P450 isoenzyme 2C9; isoenzyme 3A4 has negligible effect.
It is not metabolised by, nor does it substantially induce or inhibit most isoenzymes commonly

associated with metabolism of medicines (i.e. 1A1, 1A2, 2A6, 2B6, 2D6 or 2E1). Irbesartan does not induce or inhibit isoenzyme 3A4.

Irbesartan and its metabolites are excreted via both biliary and renal routes. About 20 % of the administered radioactivity after an oral or intravenous dose of ^{14}C irbesartan is recovered in urine, with the remainder in the faeces. Less than 2 % of the dose is excreted in urine as unchanged irbesartan.

The terminal elimination half-life ($t_{½}$) 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.

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.

In elderly (male and female) normotensive subjects (65-80 years) with clinically normal renal and hepatic function, the plasma AUC and peak plasma concentrations (Cmax) 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.

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.

In patients with renal impairment (regardless of degree) and in haemodialysis patients, the pharmacokinetics of irbesartan are not significantly altered. Irbesartan is not removed by haemodialysis.

In patients with hepatic insufficiency due to mild to moderate cirrhosis, the pharmacokinetics of irbesartan are not significantly altered.

INDICATIONS:

APROVEL is indicated for the treatment of essential hypertension. It may be used either alone or in combination with other antihypertensive agents.

APROVEL is indicated for the treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria (> 300 mg/day) in patients with Type 2 diabetes and hypertension.

CONTRAINDICATIONS:

APROVEL is contraindicated in patients who have the following:

- hypersensitivity to irbesartan or to any other component of the APROVEL formulation
- a history of angioedema related to previous therapy with ARBs or angiotensin converting enzyme inhibitors (ACEIs): These patients must never again be given these medicines
- hereditary or idiopathic angioedema
- hypertrophic obstructive cardiomyopathy (HOCM)
- severe renal function impairment (creatinine clearance less than 30 ml/min)
- moderate to severe renal impairment, and concomitantly using fluoroquinolones
- bilateral renal artery stenosis
- renal artery stenosis in patients with single kidney, or a transplanted kidney
- aortic stenosis
- concomitant therapy with potassium-sparing diuretics such as spironolactone, triamterene, amiloride

- porphyria
- lithium therapy: Concomitant administration with APROVEL may lead to toxic blood concentrations of lithium (see WARNINGS and SPECIAL PRECAUTIONS and INTERACTIONS)
- pregnancy and lactation (See WARNINGS and SPECIAL PRECAUTIONS and PREGNANCY AND LACTATION).

Paediatric Use:

Safety and efficacy in paediatric patients have not been established.

WARNINGS and SPECIAL PRECAUTIONS:

Hypotension – Volume-Depleted Patients:

APROVEL has been associated with hypotension in hypertensive patients without other co-morbid conditions. Symptomatic hypotension may be expected to occur in sodium/volume-depleted patients such as those treated vigorously with diuretics and/or salt restriction, or on haemodialysis. Volume and/or sodium-depletion should be corrected before initiating therapy with APROVEL or a lower starting dose (APROVEL 75 mg) should be considered (See DOSAGE AND DIRECTIONS FOR USE).

Renal impairment:

When APROVEL is used in patients with impaired renal function, a periodic monitoring of potassium and creatinine serum levels is recommended (see Contraindications).

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients whose renal function depends on the activity of the renin-angiotensin-aldosterone system (e.g. hypertensive patients with renal artery stenosis in one or both kidneys, or patients with severe congestive heart failure), treatment with other medicines that affect this system has been associated with oliguria and/or progressive uraemia and with acute renal failure and/or death (see CONTRAINDICATIONS).

The possibility of a similar effect occurring with the use of an angiotensin II receptor antagonist cannot be excluded.

In hypertensive type 2 diabetic patients with proteinuria (≥ 900 mg/day), i.e. a population with a high risk of renal artery stenosis, no patient treated with APROVEL in IDNT had an early acute rise in serum creatinine attributable to renal artery stenosis.

Fluoroquinolones and ARBs:

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

Lithium:

The combination of lithium and APROVEL is contraindicated (refer to CONTRAINDICATIONS and INTERACTIONS).

Hyperkalaemia:

May occur during the treatment with APROVEL, more frequently 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.

In two clinical studies of patients with hypertension and type 2 diabetic renal disease, IDNT (Irbesartan Diabetic Nephropathy Trial) and IRMA 2 (Irbesartan MicroAlbuminuria in type 2 diabetes), the following was reported:

In IDNT the percentage of subjects with hyperkalaemia (> 6 mmol/l) was 18,6 % in the APROVEL group (N = 579) compared to 6,0 % in the placebo group (N = 569).

In IRMA 2 the percentage of subjects with hyperkalaemia (> 6 mmol/l) was 1,0 % in the

APROVEL group (N = 402) and none in the placebo group (N = 206).

In IDNT, the rate of discontinuations due to hyperkalaemia in the APROVEL group was 2,1 % compared to 0,36 % in the placebo group.

In IRMA 2, the rate of discontinuations due to hyperkalaemia of patients in the APROVEL group was 0,5 % compared to none in the placebo group.

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

Lactose intolerance:

APROVEL contains lactose and should be used with caution in patients with intolerance to lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take APROVEL.

Pregnancy and lactation:

Should a woman become pregnant while receiving APROVEL, the treatment should be stopped immediately and the patient switched to a different class of medicine of which the main action does not directly affect the RAS (see CONTRAINDICATIONS and PREGNANCY AND LACTATION).

Effects on ability to drive and use machines:

APROVEL may cause dizziness and fatigue. Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving or operating machinery.

INTERACTIONS:

Concomitant use of ARBs and fluoroquinolones may precipitate acute kidney injury. The mechanism of the possible interaction between the different classes of medicines, over and above different mechanisms of kidney damage, is unknown (see CONTRAINDICATIONS).

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

APROVEL is primarily metabolised by CYP2C9, however, during clinical interaction studies, no significant pharmacodynamic interactions were observed when irbesartan was co-administered with warfarin (a medicine metabolised by CYP2C9).

APROVEL does not affect the pharmacokinetics of digoxin or simvastatin.

The pharmacokinetics of irbesartan is not affected by co-administration with nifedipine or hydrochlorothiazide.

Based on experience with the use of other medicines that affect the renin-angiotensin system, concomitant use of potassium-sparing diuretics, potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium.

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 APROVEL, may result in deterioration of renal function, including possible acute renal failure. These effects may be reversible. It is imperative that renal function be periodically monitored in patients receiving concomitant APROVEL and NSAID therapy. The antihypertensive effect of angiotensin II receptor antagonists, including APROVEL, may be attenuated by NSAIDs including selective COX-2 inhibitors.

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 reported with APROVEL. Therefore, the combination is contraindicated (see CONTRAINDICATIONS).

PREGNANCY AND LACTATION:

Pregnancy:

Safety in pregnancy and lactation has not been established (see CONTRAINDICATIONS and WARNINGS and SPECIAL PRECAUTIONS). When pregnancy is planned or confirmed, APROVEL should be discontinued.

Medicines affecting the renin-angiotensin system, such as APROVEL, can cause embryonal toxicity, foetal and neonatal morbidity and mortality when administered in pregnant women.

Women of Childbearing Potential

Women of childbearing age should ensure effective contraception.

Lactation:

Safety has not been established.

Irbesartan is excreted in the milk of lactating rats. It is not known whether irbesartan or its metabolites are excreted in human milk. A decision should be made whether to discontinue breastfeeding or to discontinue APROVEL, taking into account the importance of APROVEL to the therapy of the mother and the potential risk to the infant (see CONTRAINDICATIONS).

DOSAGE AND DIRECTIONS FOR USE:

The usual recommended initial and maintenance dose is 150 mg once daily, with or without food.

In patients insufficiently controlled with 150 mg once daily, the dose of APROVEL may be increased to 300 mg, or other anti-hypertensive agents may be added.

In patients with hypertension and type 2 diabetic renal disease, 300 mg of APROVEL once daily is the preferred maintenance dose.

Elderly Patients and Patients with Renal or Hepatic Impairment:

No dosage reduction is generally necessary in the elderly or in patients with impaired renal function or impaired hepatic function (mild to moderate degree).

Patients with Intravascular Volume Depletion:

See WARNINGS and SPECIAL PRECAUTIONS: Hypotension – volume-depleted patients.

SIDE EFFECTS:

Adverse reactions have been ranked under the heading of system-organ class and frequency using the following convention:

Very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1000, < 1/100); rare (≥ 1/10000, < 1/1000); very rare (< 1/10000), including isolated cases.

In clinical trials in patients with **hypertension**, the following adverse drug reactions were reported:

Nervous system disorders

Common: dizziness, headache

Cardiac disorders

Uncommon: tachycardia

Respiratory, thoracic and mediastinal disorders

Uncommon: cough

Gastrointestinal disorders

Common: nausea, vomiting Uncommon: diarrhoea, dyspepsia

Reproductive system and breast disorders

Uncommon: sexual dysfunction

General disorders and administration site conditions

Common: fatigue

Uncommon: chest pain

Other (frequency not specified)

Oedema

Investigations

No clinically significant changes in laboratory test parameters occurred in controlled clinical studies of hypertension.

No special monitoring of laboratory parameters is necessary for patients with essential hypertension receiving therapy with APROVEL.

In clinical trials in patients with h**ypertension and type 2 diabetic renal disease**, the following additional adverse reactions were reported:

Nervous system disorders

Common: dizziness, orthostatic dizziness

Vascular disorders

Common: orthostatic hypotension

Investigations

Very common: hyperkalaemia

Since introduction of APROVEL in the market (**post-marketing experience**), the following adverse reactions have also been reported:

Immune system disorders

Hypersensitivity reactions (urticaria, angioedema) (see CONTRAINDICATIONS)

Metabolism and nutrition disorders

Hyperkalaemia

Nervous system disorders

Headache

Hepato-biliary disorders

Increased liver function tests, jaundice, hepatitis

Renal disorders

Impaired renal function including cases of renal failure in patients at risk

Ear and labyrinth disorders

Vertigo

Other

Asthenia, myalgia

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

No specific information is available on the treatment of overdosage with APROVEL. However, daily doses of up to 900 mg/day for 8 weeks have been well tolerated. The patient should be closely monitored and treatment should be symptomatic and supportive. Suggested measures include induction of emesis and/or gastric lavage. APROVEL is not removed from the body by haemodialysis.

IDENTIFICATION:

APROVEL 75 mg, 150 mg and 300 mg tablets are white to off-white, biconvex, oval, film-coated tablets, engraved with a heart on one side and the number “2871”, “2872” and “2873” respectively on the other side.

PRESENTATION:

APROVEL tablets are packed in blister packs containing 28 tablets.

STORAGE INSTRUCTIONS:

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

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

APROVEL 75 mg tablets: 31/7.1.3/0632

APROVEL 150 mg tablets: 31/7.1.3/0633

APROVEL 300 mg tablets: 31/7.1.3/0634

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

sanofi-aventis south africa (pty) ltd

2 Bond Street

Midrand

1685

South Africa

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

23 March 2015