1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS

1. *NAME OF MEDICINAL PRODUCT*

MULTICHRIS LOSARTAN POTASSIUM 50 (LOSARTAN POTASSIUM TABLETS BP 50 MG)

2. QUALITATIVE & QUANTITATIVE COMPOSITION

Qualitative Declaration-

Each Film coated tablet contains:

Losartan Potassium BP 50 mg

Excipients Q.S.

Colour: Titanium Dioxide BP

Quantitative Declaration-

Batch Size: 100000 Tablets

S. No.	Ingredients.	References	Label Claim	Overages	Quantity/ Batch(kg)	Quantity / Tablet(mg)
1.	* Losartan Potassium	BP	50mg	–	5.000 KG	50.00 MG
2.	** Lactose	BP	–	–	8.240 KG	80.00 MG
3.	** Maize Starch	BP	–	–	4.320 KG	40.00 MG
4.	**Microcrystalline cellulose	BP	–	–	1.020 KG	10.00 MG
5.	Croscarmellose sodium	BP	–	–	0.500 KG	5.00 MG
6.	Povidone K-30%	BP	–	–	0.450 KG	4.50 MG
7.	Isopropyl Alcohol	BP	–	–	3.6 LIT	–
8.	Magnesium Stearate	BP			0.200 KG	2.00 MG
9.	Purified Talc	BP	–	–	0.300 KG	3.00 MG
10.	Colloidal silicon dioxide	BP	–	–	0.100 KG	1.00 MG
11.	Kyron T-314	USP-NF	--	--	0.450 KG	4.50 MG
	Avg. wt. of tablet		**TOTAL**		**20.000 KG**	**200MG**
COATING MATERIAL				**QTY PER BATCH.**		**UNIT**
12	Isopropyl Alcohol BP	BP	–	–	4.560 LTR	–
13	Ready mix of White (Film Coating) IHS	IHS	–	–	0.600 KG	6.00 MG
14	Methylene Chloride BP	BP	–	–	6.84 LTR	–

Note: * Compensate the qty of Actives with maize starch to maintain the average weight.

**** compensate of overages of lactose, microcrystalline cellulose and maize starch to loss on drying.**

3. PHARMACEUTICAL FORM

Tablet.

A White coloured, oval shaped, biconvex, film coated tablet having embossing of MCP on upper puh& break line on lower punch.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Treatment of essential hypertension in adults and in children and adolescents 6-18 years of age
- Treatment of renal disease in patients with hypertension and type 2 diabetes mellitus with proteinuria ≥ 0.5 g/day as part of an antihypertensive treatment.
- Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy documented by ECG (see section 5.1 LIFE study. Race).

4.2 Dosage and administration

Posology

Hypertension

The usual starting and maintenance dose is 50mg once daily for most patients. The maximal antihypertensive effect is attained 3-6 weeks after initiation of therapy. Some patients may receive an additional benefit by increasing the dose to 100mg once daily (in the morning). Losartan potassium film-coated tablets may be administered with other antihypertensive agents, especially with diuretics (e.g. hydrochlorothiazide).

Paediatric population

There are limited data on the efficacy and safety of losartan in children and adolescents aged 6-16 years old for the treatment of hypertension (see section5.1). Limited pharmacokinetic data are available in hypertensive children above one month of age.

For patients who can swallow tablets, the recommended dose is 25mg once daily in patients >20 to <50kg. In exceptional cases the dose can be increased to a maximum of 50mg once daily. Dosage should be adjusted according to blood pressure response.

In patients >50kg, the usual dose is 50mg once daily. In exceptional cases the dose can be adjusted to a maximum of 100mg once daily. Doses above 1.4mg/kg (or in excess of 100mg) daily have not been studied in pediatric patients.

Losartan is not recommended for use in children under 6 years old, as limited data are available in these patient groups.

It is not recommended in children with glomerular filtration rate <30ml/min/1.73m2, as no data are available.

Losartan is also not recommended in children with hepatic impairment.

Hypertensive type II diabetic patients with proteinuria ≥ 0.5g/day

The usual starting dose is 50 mg once daily. The dose may be increased to 100 mg once daily based on blood pressure response from one month after initiation of therapy onwards. Losartan Actavis may be administered with other antihypertensive agents (e.g. diuretics, calcium channel blockers, alpha- or beta-blockers, and centrally acting agents) as well as with insulin and other commonly used hypoglycemic agents (e.g. sulfonylureas, glitazones and glucosidase inhibitors).

Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy documented by ECG

The usual starting dose is 50 mg of Losartan Actavis once daily. A low dose of hydrochlorothiazide should be added and/ or the dose of Losartan Actavis should be increased to 100 mg once daily based on blood pressure response.

Use in patients with intravascular volume depletion

For patients with intravascular volume-depletion (e.g. those treated with high-dose diuretics), a starting dose of 25mg once daily should be considered.

Use in patients with renal impairment and haemodialysis patients

No initial dosage adjustment is necessary in patients with renal impairment and in haemodialysis patients.

Use in patients with hepatic impairment

A lower dose should be considered for patients with a history of hepatic impairment. There is no therapeutic experience in patients with severe hepatic impairment. Therefore, losartan is contraindicated in patients with severe hepatic impairment.

Use in Elderly

Although consideration should be given to initiating therapy with 25mg in patients over 75 years of age, dosage adjustment is not usually necessary for the elderly.

Method of administration-

Losartan potassium film-coated Tablets should be swallowed with a glass of water.

Losartan potassium film-coated Tablets may be administered with or without food.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Second and third trimester of pregnancy
- Severe hepatic impairment
- The concomitant use of Losartan Actavis with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m2).

4.4 Special Warnings and Precautions for Use

Hypersensitivity
Angioedema. Patients with a history of angioedema (swelling of the face, lips, throat, and/ or tongue) should be closely monitored.

Hypotension and Electrolyte/Fluid Imbalance
Symptomatic hypotension, especially after the first dose and after increasing of the dose, may occur in patients who are volume- and/or sodium-depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. These conditions should be corrected prior to administration of Losartan potassium film-coated Tablets, or a lower starting dose should be used. This also applies to children 6 to 18 years of age.

Electrolyte imbalances
Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. In a clinical study conducted in type 2 diabetic patients with nephropathy, the incidence of hyperkalemia was higher in the group treated with Losartan potassium film-coated Tablets as compared to the placebo group (see section 4.8. Therefore, the plasma concentrations of potassium as well as creatinine clearance values should be closely monitored, especially patients with heart failure and a Creatinine Clearance between 30-50ml/ min should be closely monitored.
The concomitant use of potassium sparing diuretics, potassium supplements and potassium containing salt substitutes with losartan is not recommended.

Hepatic impairment
Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, a lower dose should be considered for patients with a history of hepatic impairment. There is no therapeutic experience with losartan in patients with severe hepatic impairment. Therefore losartan must not be administered in patients with severe hepatic impairment.
Losartan is also not recommended in children with hepatic impairment.

Renal impairment
As a consequence of inhibiting the renin-angiotensin system, changes in renal function including renal failure have been reported (in particular, in patients whose renal function is dependent on the rennin angiotensin aldosterone system such as those with severe cardiac insufficiency or pre- existing renal dysfunction). As with other medicinal product that affect the renin-angiotensin- aldosterone system, increases in blood urea and serum creatinine have also been reported in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney; these changes in renal function may be reversible upon discontinuation of therapy. Losartan should be used with caution in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.

Use in paediatric patients with renal impairment
Losartan is not recommended in children with glomerular filtration rate <30ml/min/1.73m2 as no data are available.
Renal function should be regularly monitored during treatment with losartan as it may deteriorate.
This applies particularly when losartan is given in the presence of other conditions (fever, dehydration) likely to impair renal function.
Concomitant use of losartan and ACE-inhibitors has shown to impair renal function. Therefore, concomitant use is not recommended.

Renal transplantation
There is no experience in patients with recent kidney transplantation.

Primary hyperaldosteronism
Patients with primary aldosteronism generally will not respond to antihypertensive medicinal product acting through inhibition of the renin-angiotensin system. Therefore, the use of losartan tablets is not recommended.

Coronary heart disease and cerebrovascular disease
As with any antihypertensive agents, excessive blood pressure decrease in patients with ischemic cardiovascular and cerebrovascular disease could result in a myocardial infarction or stroke.

Heart failure
In patients with heart failure, with or without renal impairment, there is - as with other medicinal product acting on the renin-angiotensin system - a risk of severe arterial hypotension, and (often acute) renal impairment. There is no sufficient therapeutic experience with losartan in patients with heart failure and concomitant severe renal impairment, in patients with severe heart failure (NYHA class IV) as well as in patients with heart failure and symptomatic life threatening cardiac arrhythmias. Therefore, losartan should be used with caution in these patient groups. The combination of losartan with a beta-blocker should be used with caution.

4.5 Interaction with other Medicinal products and other forms of Interaction

Other antihypertensive agents may increase the hypotensive action of losartan. Concomitant use with other substances which may induce hypotension as an adverse reaction (like tricyclic antidepressants, antipsychotics, baclofene, amifostine): may increase the risk of hypotension,
Losartan is predominantly metabolised by cytochrome P450 (CYP) 2C9 to the active carboxylic- acid metabolite. In a clinical trial it was found that fluconazole (inhibitor of CYP2C9) decreases the exposure to the active metabolite by approximately 50%. It was found that concomitant treatment of losartan with rifampicine (inducer of metabolism enzymes) gave a 40% reduction in plasma concentration of the active metabolite. The clinical relevance of this effect is unknown. No difference in exposure was found with concomitant treatment with fluvastatin (weak inhibitor of CYP2C9).
As with other medicinal product that block angiotensin II or its effects, concomitant use of other medicinal product which retain potassium (e.g. potassium-sparing diuretics: amiloride, triamterene, spironolactone) or may increase potassium levels (e.g. heparin), potassium supplements or salt substitutes containing potassium may lead to increases in serum potassium. Co-medication is not advisable.
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Very rare cases have also been reported with angiotensin II receptor antagonists. Co-administration of lithium and losartan should be undertaken with caution. If this combination proves essential, serum lithium level monitoring is recommended during concomitant use.
When angiotensin II antagonists are administered simultaneously with NSAIDs (i.e. selective COX-2 inhibitors, acetylsalicylic acid at anti-inflammatory doses and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitant use of angiotensin II antagonists or diuretics 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.
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.

4.6 Fertility, pregnancy and lactation

Pregnancy
The use of AIIRAs is not recommended during the first trimester of pregnancy. The use of AIIRAs is contra-indicated during the second and third trimester of pregnancy.
Epidemiological evidence 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 on the risk with Angiotensin II Receptor Inhibitors (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 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).
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.

Lactation
Because no information is available regarding the use of losartan during breastfeeding, losartan 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 Effects on Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed. However, when driving vehicles or operating machinery it must be borne in mind that dizziness or drowsiness may occasionally occur when taking antihypertensive therapy, in particular during initiation of treatment or when the dose is increased.

4.8 Undesirable Effects

Losartan has been evaluated in clinical studies as follows:

- In a controlled clinical trials in > 3000 adult patients 18 years of age and older for essential hypertension,
- In a controlled clinical trial in 177 hypertensive paediatric patients 6 to 16 years of age
- In a controlled clinical trial in > 9000 hypertensive patients 55 to 80 years of age with left ventricular hypertrophy (see LIFE Study, section 5. 1)
- In a controlled clinical trial in > 7700 adult patients with chronic heart failure (see ELITE I, ELITE II and HEAAL Study, section 5.1)
- In a controlled clinical trial in > 1500 type 2 diabetic patients 31 years of age and older with proteinuria.

In these clinical trials, the most common adverse reaction was dizziness.
The frequency of adverse events listed below is defined using the following convention:
Very common (≥ 1/10);
Common (≥ 1/100 to, < 1/10);
Uncommon (≥ 1/1,000 to, < 1/100);
Rare (≥ 1/10,000 to, < 1/1,000);
Very rare (< 1/10,000),
Not known (cannot be estimated from the available data).

The following additional adverse reactions occurred more frequently in patients who received losartan than placebo (frequencies not known):back pain, urinary tract infection, and flu-like

Symptoms

Renal and urinary disorders:
As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function including renal failure have been reported in patients at risk; these changes in renal function may be reversible upon discontinuation of therapy.

Paediatric populations:
The adverse reaction profile for paediatric patients appears to be similar to that seen in adult patients.
Data in the paediatric population are limited.

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 via the Yellow Card Scheme; website: www.mhra.gov.uk/yellowcard

4.9 Overdose

Symptoms of intoxication Limited data are available with regard to overdose in humans. The most likely manifestations of overdose would be hypotension and tachycardia. Bradycardia could occur from parasympathetic (vagal) stimulation.

Treatment of intoxication
If symptomatic hypotension should occur, supportive treatment should be instituted.
Measures are depending on the time of medicinal product intake and kind and severity of symptoms. Stabilization of the circulatory system should be given priority. After oral intake the administration of a sufficient dose of activated charcoal is indicated. Afterwards, close monitoring of the vital parameters should be performed. Vital parameters should be corrected if necessary.
Neither Losartan nor the active metabolite can be removed by hemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Angiotensin II Receptor Antagonists, ATC code: C09CA01

Losartan is a synthetic oral angiotensin-II receptor (type AT_1) antagonist. Angiotensin II, a potent vasoconstrictor, is the primary active hormone of the renin/angiotensin system and an important determinant of the pathophysiology of hypertension. Angiotensin II binds to the AT_1 receptor found in many tissues (e.g. vascular smooth muscle, adrenal gland, kidneys and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone. Angiotensin II also stimulates smooth muscle cell proliferation.
Losartan selectively blocks the AT_1 receptor. *In vitro* and *in vivo* losartan and its pharmacologically active carboxylic acid metabolite E-3174 block all physiologically relevant actions of angiotensin II, regardless of the source or route of its synthesis.
Losartan does not have an agonist effect nor does it block other hormone receptors or ion channels important in cardiovascular regulation. Furthermore Losartan does not inhibit ACE (kininase II), the enzyme that degrades bradykinin. Consequently, there is no potentiation of undesirable bradykinin mediated effects.
During administration of Losartan, removal of the angiotensin II negative feedback on renin secretion leads to increased plasma renin activity (PRA). Increase in the PRA leads to an increase in angiotensin II in plasma. Despite these increases, antihypertensive activity and suppression of plasma aldosterone concentration are maintained, indicating effective angiotensin II receptor blockade. After discontinuation of Losartan, PRA and angiotensin II values fell within three days to the baseline values.
Both Losartan and its principal active metabolite have a far greater affinity for the AT_1-receptor than for the AT_2-receptor. The active metabolite is 10- to 40- times more active than Losartan on a weight for weight basis.

5.2 PHARMACOKINETIC PROPERTIES

Absorption
Following oral administration, losartan is well absorbed and undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. The systemic bioavailability of losartan tablets is approximately 33%. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3–4 hours, respectively.

Distribution
Both losartan and its active metabolite are ≥99% bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 liters.

Biotransformation
About 14% of an intravenously- or orally-administered dose of losartan is converted to its active metabolite. Following oral and intravenous administration of 14C-labeled losartan potassium, circulating plasma radioactivity primarily is attributed to losartan and its active metabolite.
Minimal conversion of losartan to its active metabolite was seen in about one percent of individuals studied.
In addition to the active metabolite, inactive metabolites are formed.

Elimination
Plasma clearance of losartan and its active metabolite is about 600mL/min and 50mL/min respectively. Renal clearance of losartan and its active metabolite is about 74mL/min and 26mL/min, respectively. When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine, and about 6% of the dose is excreted in the urine as active metabolite. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan potassium doses up to 200mg.
Following oral administration, plasma concentrations of losartan and its active metabolite decline polyexponentially with a terminal half-life of about 2 hours and 6-9 hours, respectively. During once daily dosing with 100 mg, neither losartan nor its active metabolite accumulates significantly in plasma.
Both biliary and urinary excretion contribute to the elimination of losartan and its metabolites.
Following an oral dose/intravenous administration of 14C-labeled losartan in man, about 35%/43% of radioactivity is recovered in the urine and 58%/50% in the faeces.

Characteristics in Patients
In elderly hypertensive patients the plasma concentrations of losartan and its active metabolite do not differ essentially from those found in young hypertensive patients.
In female hypertensive patients the plasma levels of losartan were up to twice as high as in male hypertensive patients, while the plasma levels of the active metabolite did not differ between men and women.
In patients with mild to moderate alcohol-induced hepatic cirrhosis, the plasma levels of losartan and its active metabolite after oral administration were respectively 5 and 1.7 times higher than in young male volunteers (see section 4.2 and 4.4).
Plasma concentrations of Losartan are not altered in patients with a creatinine clearance above 10ml/minute. Compared to patients with normal renal function, the AUC for Losartan is about 2- times higher in haemodialysis dialysis patients.
The plasma concentrations of the active metabolite are not altered in patients with renal impairment or in haemodialysis patients.
Neither Losartan nor the active metabolite can be removed by haemodialysis.

Pharmacokinetics in paediatric patients
The pharmacokinetics of losartan have been investigated in 50 hypertensive paediatric patients > 1 month to < 16 years of age following once daily oral administration of approximately 0.54 to 0.77mg/kg of losartan (mean doses). The results showed that the active metabolite is formed from losartan in all age groups. The results showed roughly similar pharmacokinetic parameters of losartan following oral administration in infants and toddlers, preschool children, school age children and adolescents. The pharmacokinetic parameters for the metabolite differed to a greater extent between the age groups. When comparing preschool children with adolescents these differences became statistically significant. Exposure in infants/ toddlers was comparatively high.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on convertional studies of general pharmacology, genotoxicity and carcinogenic potential. In repeated dose toxicity studies, the administration of losartan induced a decrease in the red blood cell parameters (erythrocytes, haemoglobin, haematocrit), a rise in urea-N in the serum and occasional rises in serum creatinine, a decrease in heart weight (without a histological correlate) and gastrointestinal changes (mucous membrane lesions, ulcers, erosions, hemorrhages). Like other substances that directly affect the renin-angiotensin system, losartan has been shown to induce adverse effects on the late foetal development, resulting in foetal death and malformations.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Lactose, Maize Starch, Microcrystalline cellulose, Croscarmellose sodium, Povidone K-30%, Isopropyl Alcohol, Magnesium Stearate, Purified Talc, Colloidal silicon dioxide, Kyron T-314, Isopropyl Alcohol, Ready mix of White (Film Coating), Methylene Chloride.

6.2 Incompatibilities

None

6.3 Shelf Life

36 Months

6.4 Special Precautions for Storage

Store at temperature below 30°C in a dry place. Protect from light. Keep out of reach of Children.

6.5 Nature and Contents of Container

2 X 14 TABLETS
14 Tablets packed in Alu/Pvc blister. 2 such blisters packed in a printed carton with pack insert. Such cartons packed in a 7 ply corrugated box.

6.6 Special Precautions for Disposal and Other Handling

No special requirements

7. *APPLICANT/HOLDER OF CERTIFICATE OF PRODUCT REGISTRATION*

MULTICHRIS PHARM & CHEMICAL COMPANY LTD.
13, QUDUS FOLAWOYI EHI CRESCENT, OFF ASHIRIGBON STREET, ISOLO, LAGOS, NIGERIA

8. *DRUG PRODUCT MANUFACTURER*

Relax Biotech Pvt. Ltd.
862 / 1, G.I.D.C. Makarpura, Vadodara – 390 010, Gujarat.

9. *NAFDAC REGISTRATION NUMBER(S)*


Composition:
Each film tablet contain:
Losartan Potassium BP 50 mg
Excipients Q.S.
Dosage: As directed by the physician.
Refer leaflet
Warning: Keep all medicines out of reach of children
Storage: Store above 30°C in a dry place.
Protect from light.
Store in the original package.
Losartan Potassium BP 50mg
NAFDAC REG NO.: B4-8652
8 90605 7 08051 9
50mg
MULTICHRIS LOSARTAN POTASSIUM TABLETS
Losartan Potassium BP 50mg
Marketed by:
MULTICHRIS PHARM & CHEMICAL COMPANY LTD.
13, Qudus Folawoyi Ehi Crescent,
Off Asirigbon Street, Isolo, Lagos, Nigeria.
Manufactured by:
RELAX BIOTECH PVT. LTD
862/1, G.I.D.C., Makarpura,
Vadodara 390010, INDIA.
MULTICHRIS LOSARTAN POTASSIUM TABLETS
Losartan Potassium BP 50mg
MULTICHRIS LOSARTAN POTASSIUM TABLETS
Losartan Potassium BP 50mg
ORAL USE
50mg
2x14 TABLETS
MULTICHRIS LOSARTAN POTASSIUM TABLETS
Losartan Potassium BP 50mg
Batch No:
Mfg. Date:
Exp. Date:
NAFDAC REG NO: B4-8652