Attachment 3

Losartan K Film Coated Tablet
Losartan Potassium 50mg

Product Description
White, film coated tablet, round, convex, side I labeled LST 50, side II labeled NPL, odorless, tasteless

Composition
Each film coated tablet contains 50 mg of Losartan Potassium

Pharmacodynamics
Angiotensin II [formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kininase II)], is a potent vasoconstrictor, the primary vasoactive hormone of the renin-angiotensin system and an important component in the pathophysiology of hypertension. It also stimulates aldosterone secretion by the adrenal cortex. Losartan and its principal active metabolite block the vasoconstrictor and aldosterone secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor found in many tissues, (e.g., vascular smooth muscle, adrenal gland). There is also an AT2 receptor found in many tissues but it is not known to be associated with cardiovascular homeostatis. Both losartan and its principal active metabolite do not exhibit any partial agonist activity at the AT1 receptor and have much greater affinity (about 1000-fold) for the AT1 receptor than for the AT2 receptor. In vitro binding studies indicate that losartan is a reversible, competitive inhibitor of the AT1 receptor. The active metabolite is 10 to 40 times more potent by weight than losartan and appears to be a reversible, non- competitive inhibitor of the AT1 receptor.

Neither losartan nor its active metabolite inhibits ACE (kininase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin); nor do they bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Pharmacokinetics
General
Losartan is an orally active agent that undergoes substantial first-pass metabolism by cytochrome P450 enzymes. It is converted, in part, to an active carboxylic acid metabolite that is responsible for most of the angiotensin II receptor antagonism that follows losartan treatment. losartan metabolites have been identified in human plasma and urine. In addition to the active carboxylic acid metabolite, several inactive metabolites are formed. Following oral and intravenous administration of 14C-labeled losartan potassium, circulating plasma radioactivity is primarily attributed to losartan and its active metabolite. *In vitro* studies indicate that cytochrome P450 2C9 and 3A4 are involved in the biotransformation of losartan to its metabolites. Minimal conversion of losartan to the active metabolite (less than 1% of the dose compared to 14% of the dose in normal subjects) was seen in about one percent of individuals studied.
The terminal half-life of losartan is about 2 hours and of the metabolite is about 6-9 hours. The pharmacokinetics of losartan and its active metabolite are linear with oral

losartan doses up to 200 mg and do not change over time. Neither losartan nor its metabolite accumulate in plasma upon repeated once-daily dosing.
Following oral administration, Losartan is well absorbed (based on absorption of radiolabeled losartan) and undergoes substantial first-pass metabolism; the systemic bioavailability of losartan is approximately 33%. About 14% of an orally-administered dose of losartan is converted to the active metabolite. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. While maximum plasma concentrations of losartan and its active metabolite are approximately equal, the AUC of the metabolite is about 4 times as great as that of losartan. A meal slows absorption of losartan and decreases its Cmax but has only minor effects on losartan AUC or on the AUC of the metabolite (about 10% decreased).
The pharmacokinetics of losartan and its active metabolite were also determined after IV doses of each component separately in healthy volunteers. The volume of distribution of losartan and the active metabolite is about 34 liters and 12 liters, respectively. Total plasma clearance of losartan and the active metabolite is about 600 mL/min and 50 mL/min, respectively, with renal clearance of about 75 mL/min and 25 mL/min, respectively. After single doses of losartan administered orally, about 4% of the dose is excreted unchanged in the urine and about 6% is excreted in urine as active metabolite. Biliary excretion contributes to the elimination of losartan and its metabolites. Following oral 14C-labeled losartan, about 35% of radioactivity is recovered in the urine and about 60% in feces.

Indications
Hypertension: Losartan is indicated for the treatment of hypertension.

Hypertensive Patients with Left Ventricular Hypertrophy: Losartan is indicated to reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy, but there is evidence that this benefit does not apply to Black patients

Nephropathy in Type 2 Diabetic Patients: Indicated for the treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria (urinary albumin to creatinine ratio ≥300 mg/g) in patients with type 2 diabetes and history of hypertension. In this population, Losartan reduces the rate of progression of nephropathy as measured by the occurrence of doubling the serum creatinine or end-stage renal disease (need for dialysis or renal transplantation) or death.

Recommended Dosage
Hypertension:
The usual starting and maintenance dose is 50 mg once daily for most patients. The maximal antihypertensive effects is attained 3-6 weeks after initiation of therapy. Some patients may receive an additional benefit by increasing the dose to 100 mg once daily.

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

No initial dosage adjustment is necessary for elderly patients or for patients with renal impairment, including patients on dialysis. A lower dose should be considered for patients with a history of hepatic impairment.

Hypertensive Patients with Left Ventricular Hypertrophy:
The usual starting dose is 50 mg once daily. A low dose of hydrochlorothiazide should be added and/or the dose of Losartan should be increased to 100 mg once daily based on blood pressure response.

Renal Protection in Type 2 Diabetic Patients with Proteinuria and Hypertension:
The usual starting dose is 50 mg once daily. The dose may be increased to 100 mg once daily based on blood pressure response. Losartan may be administered with other antihypertensive agents (eg, diuretics, calcium-channel blockers, α- or β-blockers and centrally acting agents) as well as with insulin and other commonly used hypoglycemic agents (eg, sulfonylureas, glitazones and glucosidase inhibitors).

Mode of Administration
Oral

Contraindications
Losartan is contraindicated in patients who are hypersensitive to any component of this product.

Warnings and Precautions
Warnings
Fetal/Neonatal Morbidity and Mortality
Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin converting enzyme inhibitors. When pregnancy is detected, Losartan should be discontinued as soon as possible.
The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug. These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of Losartan as soon as possible. Rarely (probably less often than once in every thousand pregnancies), no alternative to an angiotensin II receptor antagonist will be found. In these rare cases, the mother should be apprised of

the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.
If oligohyramnios is observed, Losartan should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profilling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.
Losartan potassium has been shown to produce adverse effects in rat fetuses and neonates, including decreased body weight, delayed physical and behavioral development, mortality and renal toxicity. With the exception of neonatal weight gain (which was affected at doses as low as 10 mg/kg/day), doses associated with these effects exceeded 25 mg/kg/day (approximately three times the maximum recommended human dose of 100 mg on a mg/m2 basis). These findings are attributed to drug exposure in late gestation and during lactation. Significant levels of losartan and its active metabolite were shown to be present in rat fetal plasma during late gestation and in rat milk.

Hypotension - Volume-Depleted Patients
In patients who are intravascularly volume depleted (e.g. those treated with diuretics), symptomatic hypotension may occur after initiation of therapy with Losartan. These conditions should be corrected prior to administration of Losartan, or a lower starting dose should be used.

Precautions
General
*Hypersensitivity***:** Angioedema.
Impaired Hepatic Function
Based on pharmacokinetics data which demonstrate significantly increased plasma concentrations of Losartan in cirrhotic patients, a lower dose should be considered for patients with impaired liver function.

Impaired Renal Function
As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function have been reported in susceptible individuals treated with Losartan; in some patients, these changes in renal function were reversible upon discontinuation of therapy.
In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar outcomes have been reported with Losartan. In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen

(BUN) have been reported. Similar effects have been reported with Losartan; in some patients, these effects were reversible upon discontinuation of therapy.

Electrolyte Imbalance
Electrolyte imbalance 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 proteinuria, the incidence of
hyperkalemia was higher in the group treated with Losartan as compared to the placebo group; however, few patients discontinued therapy due to hyperkalemia.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Losartan potassium was not carcinogenic when administered at maximally tolerated dosages to rats and mice for 105 and 92 weeks, respectively. Female rats given the highest dose (270 mg/kg/day) had a slightly higher incidence of pancreatic acinar adenoma. The maximally tolerated dosages (270 mg/kg/day in rats, 200 mg/kg/day in mice) provided systemic exposures for losartan and its pharmacologically active metabolite that were approximately 160- and 90-times (rats) and 30- and 15-times (mice) the exposure of a 50 kg human given 100 mg per day.
Losartan potassium was negative in the microbial mutagenesis and V-79 mammalian cell mutagenesis assays and in the *in vitro* alkaline elution and *in vitro* and *in vivo* chromosomal aberration assays. In addition, the active metabolite showed no evidence of genotoxicity in the microbial mutagenesis, *in vitro* alkaline elution, and *in vitro* chromosomal aberration assays.

Pedriatic Use
Antihypertensive effects of Losartan have been established in hypertensive pedriatic patients aged 6 to 16 years. There are no data on the effect of Losartan on blood presssure in pedriatic patients under the age of 6 or in pedriatic patients with glomerular filtration rate < 30 mL/min/1.73 m2 .

Interactions with other Medicaments
No significant drug-drug pharmacokinetic interactions have been found in interaction studies with hydrochlorothiazide, digoxin, warfarin, cimetidine and phenobarbital. Rifampin, an inducer of drug metabolism, decreased the concentration of losartan, and its active metabolite. In humans, two inhibitors of P450 3A4 have been studied. Ketoconazole did not affect the conversion of losartan to the active metabolite after intravenous administration of losartan, and erythromycin had no clinically significant effect after oral administration. Fluconazole, an inhibitor of P450 2C9, decreased active metabolite concentration and increased losartan concentration. The pharmacodynamic consequences of concomitant use of losartan and inhibitors of P450 2C9 have not been examined. Subjects who do not metabolize losartan to active metabolite have been shown to have a specific, rare defect in cytochrome P450 2C9. These data suggest that the conversion of losartan to its active metabolite is mediated primarily by P450 2C9 and not P450 3A4.

As with other drugs that block angiotensin II or its effects, concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium.

Lithium: As with other drugs which affect the excretion of sodium, lithium excretion may be reduced. Therefore, serum lithium levels should be monitored carefully if lithium salts are to be co-administered with angiotensin II receptor antagonists.

Non-steroidal Anti-Inflammatory Agents including Selective Cyclooxygenase-2 inhibitors: In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs (NSAIDs) including those that selectively inhibit cyclooxygenase-2 inhibitors (COX-2 inhibitors), the coadministration of angiotensin II receptor antagonists including losartan may result in further deterioration of renal function. These effects are usually reversible.

NSAIDs including selective COX-2 inhibitors may diminish the antihypertensive effect of angiotensin II receptor antagonists, including losartan. This interaction should be given consideration in patients taking NSAIDs including selective COX-2 inhibitors concomitantly with angiotensin II receptor antagonists.

Statement on Usage During Pregnancy and Lactation

Pregnancy

When used in pregnancy during the 2nd and 3rd trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death in the developing fetus. When pregnancy is detected, Losartan should be discontinued as soon as possible.

Although there is no experience with the use of Losartan in pregnant women, animal studies with losartan potassium have demonstrated fetal and neonatal injury and death, the mechanism of which is believed to be pharmacologically mediated through effects on the renin-angiotensin system. In humans, fetal renal perfusion, which is dependent upon the development of the renin-angiotensin system, begins in the 2nd trimester; thus, risk to the fetus increases if Losartan is administered during the 2nd or 3rd trimesters of pregnancy.

Nursing Mothers

It is not known whether losartan is excreted in human milk, but significant levels of losartan and its active metabolite were shown to be present in rat milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Adverse Effects/Undesirable Effects

Losartan has been found to be generally well tolerated for hypertension; side effects have usually been mild and transient in nature and have not required discontinuation of therapy.

In essential hypertension, dizziness was the only side effect reported as drug-related of patients treated with Losartan. In addition, dose-related orthostatic effects were seen in patients. Rarely, rash was reported.

Losartan was generally well tolerated in hypertensive patients with left ventricular hypertrophy. The most common drug related side effects were dizziness, asthenia/fatigue and vertigo.

Among patients without diabetes at baseline, there was a lower incidence of new onset diabetes mellitus with Losartan as compared to atenolol.

Losartan was generally well tolerated in type 2 diabetic patients with proteinuria. The most common drug-related side effects were asthenia/fatigue, dizziness, hypotension and hyperkalemia.

The following additional adverse reactions have been reported :
Hypersensitivity: Anaphylactic reactions, angioedema including swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, pharynx and/or tongue has been reported rarely in patients treated with losartan; some of these patients previously experienced angioedema with other drugs including ACE inhibitors. Vasculitis, including Henoch-Schoenlein purpura, has been reported rarely.

Gastrointestinal: Hepatitis (reported rarely), liver function abnormalities, vomiting.

Hematologic: Anemia, thrombocytopenia (reported rarely).
Musculoskeletal: Myalgia, arthralgia.

Nervous System/Psychiatric: Migraine, dysgeusia.

Respiratory: Cough.

Skin: Urticaria, pruritus, erythroderma, photosensitivity.

Overdose and Treatment
Limited data are available in regard to overdosage in humans. The most likely manifestation of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

Neither losartan nor its active metabolite can be removed by hemodialysis.

Storage Conditions
Store at temperature below 30ºC.

Dosage Forms and Packaging Available
Box, 3 strips @ 10 film-coated tablets.

Shelf-life
24 months

Registration Number
LOSARTAN K TABLETS 50 mg – MALXXXXXXA

Name and Address of Manufacturer
PT. Novell Pharmaceutical Laboratories
Jl. Wanaherang No. 35, Tlajung Udik,
Gunung Putri, Bogor 16962 – Indonesia

Name and Address of Product Registration Holder
Averroes Pharmaceuticals Sdn. Bhd.
11E, Level 5, Block 1
Worldwide Business Center
Jalan 13/50, Section 13
40000 Shah Alam, Selangor
Malaysia
Tel : +603 5511 8928
Fax: +603 5511 8918

Date of Revision of Package Insert
19th August 2014