Angilock®

Ambroxol hydrochloride BP

COMPOSITION
Angilock® 50 Tablet: Each film-coated tablet contains Losartan potassium USP 50 mg.

PHARMACOLOGY
Pharmacodynamics
Losartan is an oral, specific angiotensin-II receptor (type AT1) antagonist. Angiotensin II binds to the AT1 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 proliferation. Based on binding and pharmacological bioassays, it binds selectively to the AT1 receptor. In vitro and in vivo, both 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 synthesis.

During losartan administration, removal of angiotensin-II negative feedback on renin secretion leads to increased plasma renin activity. Increases in plasma renin activity lead to increases in angiotensin II in plasma. Even with these increases, antihypertensive activity and suppression of plasma aldosterone concentration are maintained, indicating effective angiotensin-II receptor blockade.

Losartan binds selectively to the AT1 receptor and does not bind to or 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, effects not directly related to blocking the AT1 receptor, such as the potentiation of bradykinin-mediated effects, the generation of oedema (losartan 1.7%, placebo 1.9%) or fatigue (losartan 3.8%, placebo 3.9%), are not associated with losartan.

Losartan has been shown to block responses to angiotensin I and angiotensin II without affecting responses to bradykinin, a finding which is consistent with the specific mechanism of action of losartan. In contrast, ACE inhibitors have been shown to block responses to angiotensin I and enhance responses to bradykinin without altering the response to angiotensin II, thus providing a pharmacodynamic distinction between losartan and ACE inhibitors.

Pharmacokinetics

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. There was no clinically significant effect on the plasma concentration profile of Losartan when the drug was administered with a standardized meal.

Distribution
Both Losartan and its active metabolite are 99% bound to plasma proteins, primarily albumin. The volume of distribution of Losartan is 34 liters. Studies in rats indicate that Losartan crosses the blood-brain barrier poorly, if at all.

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-labelled Losartan potassium, circulating plasma radioactivity primarily is attributed to Losartan and its active metabolite.
In addition to the active metabolite, inactive metabolites are formed, including two major metabolites formed by hydroxylation of the butyl side chain and a minor metabolite, an N-2 tetrazole glucuronide.

Elimination
Plasma clearance of Losartan and its active metabolite is about 600 ml/min and 50 ml/min, respectively. Renal clearance of Losartan and its active metabolite is about 74 ml/min and 26 ml/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 200 mg.
Following oral administration, plasma concentrations of Losartan and its active metabolite decline poly-exponentially 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 contributes to the elimination of Losartan and its metabolites. Following an oral dose of 14C-labelled Losartan in man, about 35% of radioactivity is recovered in the urine and 58% in the faeces.

Characteristics in patients
Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of Losartan and its active metabolite were, respectively, 5-fold and 1.7-fold greater than those seen in young male volunteers. Plasma concentrations of Losartan are not altered in patients with creatinine clearance above 10 ml/min. Compared to patients with normal renal function, the AUC for Losartan is approximately 2-fold greater in haemodialysis patients. 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 pediatric patients
The pharmacokinetics of Losartan has been investigated in 50 hypertensive pediatric patients> 1 month to < 16 years of age following once daily oral administration of approximately 0.54 to 0.77 mg/kg of Losartan (mean doses). The results showed that the active metabolite is formed from Losartan in all age groups. Pharmacokinetics of Losartan and its active metabolite were generally similar across the studied age groups and consistent with pharmacokinetic historic data in adults.

INDICATION
Angilock ® (Losartan) is indicated in the treatment of all grades of hypertension.

DOSAGE AND ADMINISTRATION
The usual starting and maintenance dose is 50 mg 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 100 mg once daily. In patients who are salt depleted corrective measures should be used before starting **Angilock ®** (Losartan) and the initial dose should be reduced to 25 mg. No dosage adjustment is necessary for patients upto 75 years of age. There is limited clinical experience in older patients and a lower
starting dose of 25 mg once daily is recommended.
No initial dosage adjustment is necessary in patients with mild renal impairment (i.e. creatinine clearance 20-50 ml/min). For patients with moderate to severe renal impairment (i.e. creatinine clearance < 20 ml/min) or patients on dialysis, a lower starting dose of 25 mg is recommended.
Angilock ® (Losartan) may be administered with other antihypertensive agents.
Angilock ® (Losartan) may be administered with or without food.

Use In Elderly
Patients upto 75 years: No initial dosage adjustment is necessary for this group of patients.
Patients over 75 years : A lower starting dose of 25 mg once daily is recommended.

CONTRAINDICATION AND PRECAUTION
It is also contraindicated to patients who are hypersensitive to any component of
this product. In patients who are intravenously volume depleted (e.g. those treated with high-dose diuretics), symptomatic hypotension may occur. These conditions should be corrected prior to administer Losartan or a lower starting dose (usually
25 mg) should be used. A lower dose should be considered for patients with a history of hepatic and renal impairment. Losartan should not be used with potassium-sparing diuretics. This product contains Lactose.

SIDE EFFECT
In controlled clinical trials in patients with essential hypertension, dizziness was the only side effect reported that occurred with an incidence greater than placebo in 1% or more of patients treated with Losartan. Rarely, rash was reported although the incidence in controlled clinical trials was less than placebo. Angioedema, involving swelling of the face, lips and / or tongue has been reported rarely in patients treated with Losartan. Serious hypotension (particularly on initiating treatment in salt-depleted patients) or renal failure (mainly in patients with renal artery stenosis) may be encountered during
Losartan treatment.

ACUTE OVERDOSE
Limited data are available regarding overdose in humans. The most likely manifestation of overdose would be hypotension and tachycardia; bradycardia
could occur from parasympathetic (vagal) stimulation.
Supportive treatment should include repletion of the intravascular volume.
Neither Losartan nor the active metabolite can be removed by hemodialysis.

DRUG INTERACTION
No drug interaction of clinical significance has been identified. Compounds which have been studied in clinical pharmacokinetic trials include hydrochlorothiazide,
digoxin, warfarin, cimetidine, ketoconazole and phenobarbital.

USE IN PREGNANCY AND LACTATION
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 aldosterone system. Losartan should not be used in pregnancy and if pregnancy is detected Losartan should be discontinued as soon as possible. It is not known whether Losartan is excreted in human breast milk. However, significant level of Losartan found in rat milk which suggests that the drug should not be used in lactating mother.

STORAGE
Store below 30°C. Protect from light & moisture. Keep out of children's reach.

HOW SUPPLIED
Angilock ® 25 Tablet: Box containing 2 x 10 / 3 x 10 / 5 x 10 / 10 x 10 tablets in blister pack.
Angilock ® 50 Tablet: Box containing 2 x 10 / 3 x 10 / 5 x 10 / 10 x 10 tablets in blister pack.

SQUARE