Angilock® Plus

Losartan Potassium USP + Hydrochlorothiazide BP

PRESENTATION

Angilock® Plus 50/12.5 tablet: Each film-coated tablet contains Losartan Potassium USP 50 mg and Hydrochlorothiazide BP 12.5 mg.

PHARMACOLOGY

Angiotensin II (formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme) 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 principle active metabolite block the vasoconstrictor and aldosterone secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor found in many tissues, (e.g. vascular smooth muscle, adrenal gland). There is also an AT_2 receptor found in many tissues but it is not known to be associated with cardiovascular homeostasis. Both Losartan and its principal active metabolite do not exhibit any partial agonist activity at the AT_1 receptor and have much greater affinity (about 1000-fold) for the AT_1 receptor than for the AT_2 receptor. In vitro binding studies indicate that Losartan is a reversible, competitive inhibitor of the AT_1 receptor. Neither Losartan nor its active metabolite inhibits ACE; nor do they bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. Indirectly, the diuretic action of hydrochlorothiazide reduces plasma volume, with consequent increase in plasma renin activity, in aldosterone secretion, in urinary potassium loss and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so coadministration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with these diuretics.

PHARMACOKINETICS

Absorption: Following oral administration, Losartan is well absorbed, with systemic bioavailability of losartan approximately 33%. Mean peak concentrations of Losartan occur at about one hour, and that of its active metabolite at about 3-4 hours.

Hydrochlorothiazide is rapidly absorbed from the gastrointestinal tract with an oral bioavailability of about 65% to 75%. Peak concentrations of Hydrochlorothiazide were reached approximately 2 hours after dosing.

Distribution: Both Losartan and its active metabolite are highly bound to plasma proteins, primarily albumin, with plasma free fractions of 1.3% and 0.2% respectively. The volume of distribution of Losartan is about 34 liters, and that of the active metabolite is about 12 liters.

Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

Metabolism: 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 oral losartan administration. Various losartan metabolites have been identified in human plasma and urine. In addition to the active carboxylic acid metabolite, several inactive metabolites are formed.

Hydrochlorothiazide is not metabolized.

Excretion: The terminal half-life of Losartan itself is about 2 hours, and that of the active metabolite, about 6-9 hours. Both biliary and urinary excretion contribute substantially to the elimination of Losartan and its metabolites.

Hydrochlorothiazide is eliminated rapidly by the kidney. The plasma half-life is 5.6–14.8 hours. At least 61% of the oral dose is eliminated unchanged within 24 hours.

INDICATIONS

Hypertension: **Angilock® Plus** is indicated for the treatment of hypertension. This fixed dose combination is not indicated for initial therapy of hypertension, except when the hypertension is severe enough that the value of achieving prompt blood pressure control exceeds the risk of initiating combination therapy in these patients.

Hypertensive patients with Left Ventricular Hypertrophy: **Angilock® Plus** is indicated to reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy.

DOSAGE & ADMINISTRATIO

Hypertension: The usual starting dose is **Angilock® Plus** 50/12.5 one tablet once daily. More than two tablets of **Angilock® Plus** 50/12.5 or one tablet of **Angilock® Plus** 100/25 once daily is not recommended. Maximum antihypertensive effect is attained about three weeks after initiation of therapy. Patients whose blood pressure is not adequately controlled with losartan or hydrochlorothiazide monotherapy, may be switched to **Angilock® Plus** 50/12.5 once daily. If blood pressure remains uncontrolled after about three weeks of therapy, the dose may be increased to one tablet of **Angilock® Plus** 100/12.5 or two tablets of **Angilock® Plus** 50/12.5 or one **Angilock® Plus** 100/25 once daily. Patients whose blood pressure is not adequately controlled with losartan 100 mg monotherapy, may be switched to **Angilock® Plus** 100/12.5 once daily. If blood pressure remains uncontrolled after about three weeks of therapy, the dose may be increased to 2 tablets of **Angilock® Plus** 50/12.5 or one **Angilock® Plus** 100/25 once daily.

Severe hypertension: The starting dose of **Angilock® Plus** for initial treatment of severe hypertension is one tablet of **Angilock® Plus** 50/12.5 once daily. For patients who do not respond adequately to **Angilock® Plus** 50/12.5 after 2 to 4 weeks of therapy, the dosage may be increased to one tablet of **Angilock® Plus** 100/25 once daily. The maximum dose is one tablet of **Angilock® Plus** 100/25 once daily. It is not recommended for use as initial therapy in patients with intravascular volume depletion (e.g., patients treated with diuretics).

Hypertensive Patients with Left Ventricular Hypertrophy: Treatment should be initiated with **Angilock®** 50 mg once daily. **Angilock® Plus** 50/12.5 substituted if the blood pressure reduction is inadequate. If additional blood pressure reduction is needed, **Angilock® Plus** 100/12.5 may be substituted, followed by **Angilock® Plus** 100/25. For further blood pressure reduction other antihypertensives should be added. **Angilock® Plus** may be administered with other antihypertensive agents. **Angilock® Plus** may be administered with or without food.

Patients with Renal Impairment: The usual regimens of therapy with **Angilock® Plus** may be followed as long as the patient's creatinine clearance is greater than 30 mL/min. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so **Angilock® Plus** is not recommended.

Patients with Hepatic Impairment: **Angilock® Plus** is not recommended for titration in patients with hepatic impairment because the appropriate 25 mg starting dose of Losartan cannot be given.

CONTRAINDICATION

This combination is contraindicated in patients who are hypersensitive to any component of this product. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs. Do not co-administer aliskiren with this combination in patients with diabetes.

PRECAUTION

Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy. Because losartan decreases uric acid, losartan in combination with hydrochlorothiazide attenuates the diuretic-induced hyperuricemia. In diabetic patients, dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

SIDE EFFECTS

Abdominal pain, Edema/swelling, Palpitation, Back pain, Dizziness, Cough, Sinusitis, Upper respiratory tract infection, rash etc.

OVERDOSE

Losartan Potassium: 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 occur, supportive treatment should be instituted. Neither Losartan nor its active metabolite can be removed by hemodialysis.

Hydrochlorothiazide: The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias. The degree to which Hydrochlorothiazide is removed by hemodialysis has not been established.

DRUG INTERACTION

Losartan Potassium: There is no pharmacokinetic interaction between Losartan and hydrochlorothiazide. 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. Serum lithium level should be monitored during concomitant use with Losartan. Renal function should be monitored periodically in patients receiving Losartan and NSAID therapy. The antihypertensive effect of angiotensin II receptor antagonists, including losartan, may be attenuated by NSAIDs, including selective COX-2 inhibitors. Dual blockade of the RAS with angiotensin receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, syncope, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. Closely monitor blood pressure, renal function, and electrolytes in patients on losartan and other agents that affect the RAS. Do not co-administer aliskiren with losartan in patients with diabetes. Avoid use of aliskiren with Losartan in patients with renal impairment (GFR <60 ml/min).

Hydrochlorothiazide: When administered concurrently the following drugs may interact with thiazide diuretics: Alcohol, barbiturates or narcotics: potentiation of orthostatic hypotension may occur. Antidiabetic drugs (oral agents and insulin): dosage adjustment of the antidiabetic drug may be required. Other antihypertensive drugs: Additive effect or potentiation. Cholestyramine and colestipol resins: Absorption of Hydrochlorothiazide is impaired in the presence of anionic exchange resins.

USE IN PREGNANCY AND LACTATION

Pregnancy Category D. 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. Thiazides appear in human 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.

USE IN PAEDIATRIC PATIENTS

The safety and effectiveness in paediatric patients have not been established.

STORAGE

Store below 30° C, protected from light & moisture. Keep out of the reach of children.

HOW SUPPLIED

Angilock® Plus 50/12.5 tablet: Box containing 50 tablets in blister pack.

Manufactured by

SQUARE
PHARMACEUTICALS LTD.
BANGLADESH