LORAZ

Film coated tablet

Not used during pregnancy as it may cause injury or death to the fetus.

Composition: Each film coated tablet contains:
Active Ingredients: Losartan potassium 50 mg and Hydrochlorothiazide 12.5mg.
Inactive ingredients: Microcrystalline cellulose, Pregelatinized starch, Magnesium stearate, crosspovidone, hydroxypropyl methyl cellulose, polyethylene glycol, polysorbate, Titanium dioxide,maize starch, aerosil 200, polyoxyl 40 stearate.
Pharmaceutical form: Film Coated Tablets.
Indications: ***Hypertension:*** **Loraz** 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: **Loraz** 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.
Dosage and Administration: Loraz can be taken before, during and after meals.
The usual starting and maintenance dosage is one tablet of **Loraz** once daily. If necessary, the dosage may be increased to a maximum of two tablets of Loraz daily. The dosage however should be individualized. If patient will be treated with Loraz after monotherapy with a diuretic drug, the diuretic should be stopped 2-3 day before begining treatment by **Loraz.**
No initial dosage adjustment is necessary for elderly patients.
Contraindications:
• Patients who are hypersensitive to any component of this product.
• Patients who are hypersensitive to other sulfonamide-derived drugs.
• Patients with anuria.
• The concomittant use of Loraz with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment(GFR<60ml/min/1.73m^2)
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, Loraz 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 **Loraz** 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 mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment. If oligohydramnios is observed, **Loraz** should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (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.Thiazides cross the placental barrier and appear in cord blood. There is a risk of fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.
Dual Blockage of the rennin-angiotensin-aldosterone system(RAAS): there is evidence that the concomitant use of ACE-inhibitors,angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalemia and decresed renal function(including acute renal failure).Dual blockade of RAAS through the combined use of ACE inhibitors,angiotensin II receptor blockers or aliskiren is therefore not recommended.If dual blockade therapy is considered absolutely necessary,this should only occur under specialist supervision and subject to frequent close monitoring of renal function,electrolytes and blood pressure.ACE inhibitors,angiotensin II receptor blockes should not be used concomitantly in patients with diabetic nephropathy.
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 **Loraz.** This condition should be corrected prior to administration of **Loraz .**
Impaired Hepatic Function: Losartan Potassium-Hydrochlorothiazid, **Loraz** is not recommended for patients with hepatic impairment who require titration with losartan. The lower starting dose of losartan recommended for use in patients with hepatic impairment cannot be given using **Loraz.**
Hydrochlorothiazide:Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.
Hypersensitivity Reaction; Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.
Systemic Lupus Erythematosus; Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.
Lithium Interaction; Lithium generally should not be given with thiazides.
Precautions; *General :*
Hypersensitivity: Angioedema.
Hydrochlorothiazide: 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: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion,seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.
Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy.Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability).
Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis. Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.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.The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient.If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy.Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.
Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.
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 BUN have been reported. Similar effects have been reported with losartan; in some patients, these effects were reversible upon discontinuation of therapy.
Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.
Interaction with other Medicaments and other form of Interaction:
Losartan: *Other hypertensives:*
Concurrent use with other antihypertensives may potentiate the antihypertensive effect. No drug interactions of clinical significance have been identified. Compounds which have been studied in clinical pharmacokinetic trials include hydrochlorothiazide, digoxin, warfarin, cimetidine and Phenobarbital.
Lithium: Lithium excretion may be reduced. That is why serum lithium levels should be monitored carefully when administering lithium salts.
Hydrochlorothiazides:
When given concurrently with the following drugs, interactions may occur.
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 Antihyperyensive Drugs: Additive effect.
Cholestyramine and Colestipol Resins: Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.
Corticosteroids,ACTH: Intensified electrolyte depletion, particularly hypokalemia may occur.
Pressor Amines (e.g. Epinephrine): Possible decreased response to pressor amines but not sufficient to preclude their use.
Skeletal Muscle Relaxants, Nondepolarizing(e.g. tubocurarine): Possible increase responsiveness to the muscle relaxant.
Lithium: Diuretic agents reduce the renal clearance of lithium and add a high,risk of lithium toxicity. Concomitant use is not recommended.
Prostaglandin Synthetase Inhibitors: In some patients, the administration of a non – steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of diuretics.
Drug/Laboratory Test Interactions: Although no specific research has been performed it is to be expected that serum potassium could increase with concomitant use of potassium supplements and salt substitutes containing potassium, particularly in patients with renal impairment.Because of their effects on calcium metabolism, thiazides may interfere with tests for parathyroid function.
Pregnancy and lactation:
Use during pregnancy:
Don't take this product if you are pregnant because it can cause fetal and neonatal morbidity and death. On the basis of the pharmacologic action of losartan, harmfulness due to use in pregnancy is possible. The mechanism of this is believed to be pharmacologically mediated through the effects of rennin-angiotensin system.Fetal and neonatal morbidity and mortality can be caused by ACE inhibitors when administered to pregnant women during the second and third trimesters of pregnancy. Use of drugs that directly act on the rennin-angiotensin system during this period have been associated with fetal and neonatal disorders, including hypotension, renal insufficiency, hyperkalemia and/or skull hypoplasia. As a result of reduced renal function, oligohydramnios may occur in the fetus. This may lead to limb contractures, cranio-facial deformations and hypoplastic lung development. While no data are available, this could also occur with angiotensin II receptors antagonists.
The routine use of diuretics in otherwise healthy pregnant women is not recommended and exposes mother and fetus to unnecessary hazard. Diuretics do not prevent development of toxemia of pregnancy and there is no satisfactory evidence that they are useful in the treatment of toxemia.
From clinical observations it has appeared that thiazides may be harmful to the fetus. Thiazides cross the placental barrier and appear in the cord blood. The possible hazards to the fetus include fetal or neonatal jaundice, thrombocytopenia and possibly other adversereactions which have occurred in the adult.If children are desired and in case of pregnancy, Loraz should be discontinued as soon as possible. Furthermore, patient should immediately contact the treating physician in order to decide on an alternative treatment. It would be wise to point this out to patient at the start of treatment.
Use during Lactation: Thiazides appear in human milk. It is not known whether losartan is excreted in human milk. However, 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.
Effects on Ability to Drive and Use Machines: There are no known data on the effect on the ability to drive. In view of the possible occurrence of the side effect dizziness, one should take a negative effect on the ability to drive and operate machines into account.
Adverse Reactions:
The following adverse reported with losartan – hydrochlorothiazide occurred in ≥1 % of the patients: Abdominal pain, Edema/Swelling, Palpitation, Back pain, Dizziness, Cough, Sinusitis, Upper Respiratory Infection and Skin Rash.
The following adverse events were also reported at a rate of 1% or greater : asthenia/fatigue, diarrhea, nausea, headache, bronchitis and pharyngitis.
Adverse events occurred at about the same rate in men and women. Adverse events were somewhat more frequent in the elderly compared to non-elderly patients and somewhat more frequent in Blacks compared to non-Blacks.
Also the side effects of the separate ingredients should be taken into account:
Losartan Potassium
Other adverse experiences that have been reported with losartan, without regard to causality, are listed below; Body as a Whole: chest pain, facial edema, fever, orthostatic effects, syncope; Cardiovascular: angina pectoris, arrhythmias including atrial fibrillation, sinus bradycardia, tachycardia, ventricular tachycardia and ventricular fibrillation, CVA, hypotension, myocardial infarction, second degree AV block; Digestive: anorexia, constipation, dental pain, dry mouth, dyspepsia, flatulence, gastritis, vomiting; Hematologic: anemia; Metabolic: gout; Musculoskeletal: arm pain, arthralgia, arthritis, fibromyalgia, hip pain, joint swelling, knee pain, leg pain, muscle cramps, muscle weakness, musculoskeletal pain, myalgia, shoulder pain, stiffness; Nervous System/Psychiatric: anxiety, anxiety disorder, ataxia, confusion, depression, dream abnormality, hypesthesia, insomnia, libido decreased, memory impairment, migraine, nervousness, panic disorder, paresthesia, peripheral neuropathy, sleep disorder, somnolence, tremor, vertigo; Respiratory: dyspnea, epistaxis, nasal congestion, pharyngeal discomfort, respiratory congestion, rhinitis, sinus disorder; Skin: alopecia, dermatitis, dry skin, ecchymosis, erythema, flushing, photosensitivity, pruritus, sweating, urticaria; Special Senses: blurred vision, burning/stinging in the eye, conjunctivitis, decrease in visual acuity, taste perversion, tinnitus; Urogenital: impotence, nocturia, urinary frequency, urinary tract infection.
Hydrochlorothiazide: Other adverse experiences that have been reported with hydrochlorothiazide, without regard to causality, are listed below:
Body as a Whole: weakness; Digestive: pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation; Hematologic: aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia; Hypersensitivity: purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions; Metabolic: hyperglycemia, glycosuria, hyperuricemia; Musculoskeletal:muscle spasm; Nervous System/Psychiatric: restlessness; Renal: renal failure, renal dysfunction, interstitial nephritis; Skin: erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis; Special Senses: transient blurred vision, xanthopsia. Persistent dry cough (with an incidence of a few percent) has been associated with ACE-inhibitor use and in practice can be a cause of discontinuation of ACE-inhibitor therapy.
Post-Marketing Experience
The following additional adverse reactions have been reported in post-marketing experience:
Digestive: Hepatitis has been reported rarely in patients treated with losartan.
Hemic: Thrombocytopenia.
Hypersensitivity: 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-Schönlein
purpura, has been reported with losartan. Anaphylactic reactions have been reported.
Metabolic and Nutrition: Hyperkalemia, hyponatremia have been reported with losartan.
Musculoskeletal: Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.
Respiratory: Dry cough (see above) has been reported with losartan.
Skin: Erythroderma has been reported with losartan.

16x24
V05

لـوراز

أقراص مغلفة

لا يستخدم أثناء الحمل حيث أنه قد يسبب إصابة أو وفاة للجنين.

بيان التركيب : كل قرص مغلف يحتوي علي:

المواد الفعالة: لوزارتان بوتاسيوم ٥٠ مجم / هيدروكلورثيازيد ١٢,٥مجم

المواد الغير فعالة: ميكروكريستالين سيليلوز، نشا، ستيرات الماغنسيوم، كروسبوفيدون، هيدروكسى بروبايل ميثيل سليلوز، بولياثيلين جلايكول، بوليسوربات، تايتانيم ثنائى الأكسيد، نشا ذرة، إيروسيل ٢٠٠، بولىأوكسيل ٤٠ ستياريت.

ماهو لوراز وماهو إستخدامه؟ يحتوى **لوراز** علي لوزارتان بوتاسيوم الذى ينتمى إلى مجموعة سد مستقبلات الإنجيوتنسين، و هيدروكلورثيازيد مدر للبول.

دواعى الإستعمال: يستخدم لوراز في الحالات الآتية:

- خفض ارتفاع ضغط الدم. لا يستخدم فى بداية علاج ارتفاع ضغط الدم.
- يقلل من فرصة حدوث السكتة الدماغية فى مرضى إرتفاع ضغط الدم و مشاكل القلب (تضخم البطين الأيسر)، **لوراز** قد لا يساعد المرضى السود فى هذه المشكلة.

☐ لا توجد دراسات علي إستخدام **لوراز** لأقل من ١٨ سنة.

☐ لوزارتان يساعد علي إرتخاء الأوعية الدموية مما يقلل إرتفاع ضغط الدم.

هيدروكلورثيازيد يجعل الكلى تمرر كمية أكبر من المياه والأملاح.

لا تتناول لوراز: لا تتناول **لوراز** في الحالات التالية:

- الحساسية لأى من مكونات المستحضر.
- الحساسية لأى دواء يحتوى على سالفونأميدز.
- عدم التبول.
- تعانى من داء السكرى أو إختلال وظائف الكلى و تعالج بمخفض لإرتفاع ضغط الدم يحتوى على اليسكرين.

قبل تناول لوراز: إعلم الطبيب المعالج فى الحالات التالية:

- الحمل أو التخطيط للحمل.
- الرضاعة الطبيعية، **لوراز** يمكن أن يمر إلى لبن الأم و يسبب ضرر للطفل.
- وجود قيء، إسهال ، العرق الكثير أو عدم شرب سوائل بكمية كافية. هذه ممكن تؤدى إلى إنخفاض ضغط الدم.
- مشاكل في الكبد.
- مشاكل في الكلى.
- الذأب الإحمرارى.
- الداء السكرى,ربو,نقرس,أي نوع من الحساسية.

تناول أدوية أخرى: يجب إبلاغ الطبيب في حالة تناول أى دواء أخر ويشمل الأدوية الموصوفة بتذكرة طبية أو من غير تذكرة طبية والفيتامينات و أدوية الأعشاب.

إبلغ الطبيب في حالة تناول أى من الأدوية التالية:

- البوتاسيوم، بدائل الأملاح التي تحتوى علي بوتاسيوم، مدرات البول، ليثيوم، الإدوية المضادة للإلتهابات و الألم و التهابات المفاصل(مضادات الالتهاب الخالية من الإستيروبد) وتشمل أيضاً مثبطات كوكس٢، و الأدوية الأخرى المخفضة لضغط الدم.الطبيب قد يحتاج الى تغيير جرعة و/أو تناول دواء أخر.في حالة تناول سد مستقبلات الانجيوتنسين أو مثبطات الإنزيم المحول للإنجيوتنسين.الأدوية الأخرى المخفضة لضغط الدم.

كيفية تناول لوراز:

☐ يجب تناول **لوراز** كما وصف الطبيب.

☐ يمكن تناول **لوراز** مع الطعام أو بدون الطعام.

☐ فى حالة نسيان جرعة تناولها عند التذكر. في حالة إقتراب موعد الجرعة التالية لا تتناول الجرعة المنسية. فقط تناول الجرعة التالية في ميعادها المعتاد.

☐ فى حالة تناول جرعة زائدة أبلغ الطبيب أو توجه إلى أقرب مستشفى.

☐ يمكن للطبيب عمل تحاليل للدم من وقت لأخر أثناء تناول لوراز .

الآثار الجانبية:يمكن حدوث الآثار الجانبية التالية مع **لوراز** التي قد تكون خطيرة.

- إصابة أو موت للجنين.
- حساسية وأعراضها تورم الوجه، الشفاه ،الحلق أو اللسان. أوقف تناول **لوراز** و أستشر الطبيب فورا.
- إنخفاض ضغط الدم مما قد يسبب إغماء أو دوخة.
- ظهور أو تفاقم حالة الذأب الإحمرارى.
- في حالة وجود مشاكل بالكلى يمكن حدوث تدهور في عمل الكلى. أبلغ الطبيب في حالة تورم القدمين، الكاحل، اليدين أو زيادة في الوزن غير مبررة.
- في حالة وجود مشاكل بالكبد يمكن حدوث تدهور في عمل الكبد. أبلغ الطبيب إذا كان لديك غثيان، ألم في الجانب الأيمن الأعلى من المعدة، إصفرار العين أو الجلد (يمكن أن يكون مصاحب بحكة)

الآثار الجانبية المألوفة **للوراز** مع مرضى إرتفاع ضغط الدم :

- الزكام (إلتهاب الجهاز التنفسي الاعلي)، إنسداد الأنف.
- دوخة.
- ألم بالظهر.
- سرعة أو إضطراب ضربات القلب.
- طفح جلدى.

إبلغ الطبيب في حالة ظهور أثار جانبية تزعجك.

العبوة: لوراز: عبوة كرتون بها شريطين (الو/بي في سي) بكل منهما ٧ اقراص مغلفة ونشرة مرفقة.

ظروف التخزين : يحفظ في درجة حرارة لا تتعدي ٣٠ درجة مئوية في مكان جاف، يحفظ بعيدا عن متناول الاطفال.

إنتاج:

المجموعة المصرية للصناعات الدوائية

EGPI

Laboratory Test Findings:

Creatinine, Blood Urea Nitrogen: Minor increases in blood urea nitrogen (BUN) or serum creatinine were observed in 0,6 and 0,8 %, respectively, of patients with essential hypertension treated with losartan- Hydrochlorothiazide alone.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.14 grams percent and 0.72 volume percent, respectively) occurred frequently in patients treated with losartan- Hydrochlorothiazide alone, but were rarely of clinical importance. No .patients were discontinued due to anemia

Liver Function Tests: Occasional elevations of liver enzymes and/or serum bilirubin have occurred. In patients with essential hypertension treated with losartan- Hydrochlorothiazide alone, no patients were discontinued due to these laboratory adverse experiences.

Serum Electrolytes: See **PRECAUTIONS.**

Overdose: No specific information is available on the treatment of overdosage. Treatment is symptomatic and supportive. Therapy with **loraz** should be discontinued and the patient observed closely. Suggested measures include induction of emesis and/or gastric lavage if ingestion is recent, and correction of dehydration, electrolyte imbalance and hypotension by established procedures.

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. 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.

Pharmacological propereties:

Pharmacodynamic Properties:The components of Loraz have been shown to have an additive effect on blood pressure reduction, reducing blood pressure to a greater degree than either component alone. This effect is thought to be a result of the complimentary actions of both components. As a result of its diuretic effect, hydrochlorothiazide increases plasma renin activity, aldosterone secretion and the levels of angiotensin II and decreases serum potassium, while losartan blocks all physiologically relevant effects of angiotensin II, including inhibition of aldosterone secretion, this could attenuate the potassium loss associated with the use of hydrochlorothiazide. Generally losartan causes a slight decrease in serum uric acid which is persistent in chronic therapy. Hydrochlorothiazide has

been shown to cause modest increases in uric acid. When the combination was used, an elevation of uric acid was observed, although somewhat less frequently than with hydrochlorothiazide alone.

The antihypertensive effect of **Loraz** is sustained for 24 hour period. Administration of Loraz had no clinically significant effect on heart rate. **Loraz** is effective in reducing blood pressure in males and females,blacks and non-blacks and younger(<65 years) and older(≥ 65 years) patients and is not only effective in mild but also severe hypertension.

Losartan: Losartan belongs to a new class of antihypertensives and is an effective, synthetic, orally active angiotensin II receptor antagonist. angiotensin II, a potent vasoconstrictor, is the active hormone of the rennin-angiotensin system and a major determinant in the pathophysiology of hypertension. Angiotensin II also stimulates smooth muscle cell proliferation. Angiotensin II binds to the AT1 receptor found in many tissues (e.g. vascular smooth muscles, adrenal gland, kidneys, and the heart), and elicits several important biological actions, including vasoconstriction and the release of aldosterone. AT2 receptors are not blocked by losartan.

Both losartan and the pharmacologically active metabolite bind selectively to the AT1 receptor. Losartan and its active metabolite have no agonist effects. Losartan does not bind to or block other hormone receptors or ion channels important in cardiovascular regulation. Losartan differs from ACE inhibitors in that it does not inhibit ACE (kininase II) the enzyme that degrades bradykinin.Losartan has no effect on autonomic reflexes and no sustained effect on plasma norepinephrine.

Hydrochlorothiazide: Hydrochlorothiazide is a diuretic and an antihypertensive. The mechanism of the antihypertensive effect of thiazides is unknown. Thiazides do not usually affect normal blood pressure. The diuretic action affects the distal renal tubular mechanism of electrolyte reabsorption.

Hydrochlorothiazide increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium and bicarbonate. After oral use, dieresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours.

Pharmacokinetics:

Absorption:

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

Here was no clinically significant effect on the plasma concentration profile of losartan when the drug was administered with a standardized meal. The effect of food on

the plasma concentration profile of losartan in this formula has not been established.

Hydrochlorothiazide: Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. The plasma half-life of hydrochlorothiazide is 5.6- 14.8 hours when the plasma levels can be followed for at least 24 hours. At least 61% of the oral dose is eliminated unchanged within 24 hours.

Distribution:

Losartan: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.

Hydrochlorothiazide: Hydrochlorothiazide crosses the placenta but not the blood- brain barrier.

Hydrochlorothiazide is excreted in human milk.

Biotransformation:

Losartan: About 14% of an intravenously – or orally- administered dose of losartan is converted to its active metabolite. Following oral and intravenous administration of C-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 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.

Hydrochlorothiazide: Hydrochlorothiazide is not metabolized.

Elimination:

Losartan: Plasma clearance of losartan and its active metabolites is about 600 ml/min and 50 ml/min, respectively. Renal clearance of losartan and its active metabolites is about 74 ml/min and 26 ml/min, respectively.

When losartan is administerd 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.

The terminal half life of losartan and the active metabolite is about 2 hours and 6-9 hours, respectively. During once daily dosing, 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 of C-labeled losartan in man, about 35% of radioactivity is recovered in the urine and 58% in the feces.

Hydrochlorothiazide: Hydrochlorothiazide is eliminated rapidly by the kidney. The plasma half life has been observed to vary between 5.6 and 14.8 hours. At least 61% of the oral dose is eliminated unchanged within 24 hours.

Characteristics in patients

Losartan: The plasma concentrations of losartan and its active metabolite in elderly hypertensives are not statistically significantly different from those in young hypertensives. The plasma concentrations of losartan in hypertensive patients are statistically significantly higher in women in comparison with men. Concentrations of the active metabolite are similar in men and women,Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolites were respectively, 5-fold and 1.7 fold greater than those seen in young male volunteers. Neither losartan nor the active metabolite can be removed by hemodialysis.

Hydrochlorothiazide:The plasma concentrations of hydrochlorothiazide in hypertensive patients with reduced renal function are statistically significant higher in comparison to patients with normal renal function.

Package: Loraz tablets: Carton box containing 2 (Al/PVC) strips each strip contains 7 film coated tablets, with inner leaflet.

Storge: Storage temperature not exceeding 30ºC in a dry place, Keep out of reach of children.

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