

LOSARTAN AND HYDROCHLOROTHIAZIDE (Systemic)

Antihypertensive.

Indications

Accepted

Hypertension (treatment)³Losartan and hydrochlorothiazide combination is indicated for the treatment of hypertension. 1

Fixed-dosage combinations are generally not recommended for initial therapy 1 and are useful for subsequent therapy only when the proportion of the component agents corresponds to the dose of the individual agents, as determined by titration.

Precautions to Consider

Cross-sensitivity and/or related problems

Patients sensitive to sulfonamide-type medications may be sensitive to this medication also. 1

Carcinogenicity

No carcinogenicity studies have been conducted with losartan and hydrochlorothiazide combination. 1

Losartan³Losartan was not carcinogenic in rats and mice given maximally tolerated doses of 270 mg per kg of body weight (mg/kg) per day and 200 mg/kg per day, respectively, for 105 and 92 weeks, respectively. 1 However, female rats had a slightly higher incidence of pancreatic acinar adenoma. 1 The maximally tolerated doses of losartan provided systemic exposures of up to 160 times (rats) and 30 times (mice) the exposure of a 50 kg human given 100 mg per day. 1

Hydrochlorothiazide³No evidence of carcinogenicity was found in two-year feeding studies at doses of up to approximately 600 mg/kg per day in female mice and 100 mg/kg per day in male and female rats. 1 However, evidence was equivocal for hepatocarcinogenicity in male mice. 1

Mutagenicity

Losartan and hydrochlorothiazide combination was not mutagenic when tested at a weight ratio of 4:1 in the Ames microbial mutagenesis assay and the V-79 Chinese hamster lung cell mutagenesis assay. 1 In addition, there was no evidence of direct genotoxicity in the in vitro alkaline elution assay in rat hepatocytes and in vitro chromosomal aberration assay in Chinese hamster ovary cells at noncytotoxic concentrations. 1

Losartan³Losartan was not mutagenic in a number of in vitro and in vivo assays. 1

Hydrochlorothiazide³Positive test results were obtained in the in vitro CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays at hydrochlorothiazide

concentrations from 43 to 1300 mcg per mL, and in the *Aspergillus nidulans* non-disjunction assay at an unspecified concentration. 1 Other mutagenicity tests were negative. 1

Pregnancy/Reproduction

Fertility: Losartan and hydrochlorothiazide combination did not affect fertility or mating behavior of male rats at dosages up to 135 mg/kg per day of losartan and 33.75 mg/kg per day of hydrochlorothiazide. 1 These doses reflect systemic exposures (AUCs) of approximately 60, 60, and 30 times, respectively, for losartan, its active metabolite, and hydrochlorothiazide, greater than those achieved in humans with losartan and hydrochlorothiazide combination (100 mg/25 mg). 1 However, administration of losartan and hydrochlorothiazide combination to female rats at doses as low as 10 mg/kg per day of losartan and 2.5 mg/kg per day of hydrochlorothiazide resulted in slight but statistically significant decreases in fecundity and fertility indices. 1 These doses were approximately 6, 2, and 2 times, respectively, for losartan, its active metabolite, and hydrochlorothiazide, greater than those achieved in humans with 100 mg of losartan and 25 mg of hydrochlorothiazide. 1

Losartan: Studies in male rats given oral doses of up to 150 mg/kg per day did not reveal adverse effects on fertility or reproductive performance. 1 However, toxic doses of 300 and 200 mg/kg per day given to females resulted in significant decreases in the number of corpora lutea, implants, and live fetuses. 1 The relationship of these findings to losartan is uncertain. 1

Hydrochlorothiazide: Hydrochlorothiazide did not produce adverse effects on the fertility of mice and rats of either sex at doses up to 100 mg/kg and 4 mg/kg, respectively. 1

Pregnancy: Medications affecting the renin-angiotensin system, such as losartan, can cause fetal and neonatal morbidity and mortality when administered to pregnant women. 1 Losartan and hydrochlorothiazide combination should be discontinued as soon as possible when pregnancy is detected. 1

Fetal exposure to medications affecting the renin-angiotensin system during the second and third trimesters of pregnancy have been associated with hypotension, neonatal skull hypoplasia, anuria, renal failure, and even death in the newborn. 1 Maternal oligohydramnios has also been reported, probably reflecting decreasing fetal renal function. 1 Oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. 1 Prematurity, intrauterine growth retardation, and patent ductus arteriosus also have been reported. 1 However, it is not clear that these occurrences were related to drug exposure. 1

It is recommended that infants exposed in utero to losartan and hydrochlorothiazide combination be closely observed for hypotension, oliguria, and hyperkalemia. 1 Oliguria should be treated with support of blood pressure and renal perfusion. 1 If oligohydramnios is observed, losartan and hydrochlorothiazide combination should be discontinued unless it is considered lifesaving for the mother. 1 Oligohydramnios, however, may not appear until after the fetus has sustained irreversible damage. 1

Losartan and hydrochlorothiazide combination was not teratogenic in rats or rabbits given a maximum dose of 10 mg/kg per day of losartan and 2.5 mg/kg per day of hydrochlorothiazide. 1 In female rats treated prior to and throughout gestation with 10 mg/kg per day of losartan and 2.5 mg/kg per day of hydrochlorothiazide, a slight increase in supernumerary ribs was observed. 1

Losartan and hydrochlorothiazide combination exposure during late gestation at doses of 50 mg/kg per day of losartan and 12.5 mg/kg per day of hydrochlorothiazide produced adverse fetal and neonatal effects in rats, including decreased body weight, renal toxicity, and mortality. 1

Hydrochlorothiazide: Thiazide diuretics cross the placenta and appear in cord blood. 1 There is a risk of fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse effects. 1

FDA Pregnancy Category C (first trimester) and D (second and third trimesters). 1

Breast-feeding

It is not known whether losartan is distributed into breast milk. 1 However, significant concentrations of losartan and its active metabolite are present in the milk of rats. 1 Thiazide diuretics are distributed into breast milk. 1

Pediatrics

No information is available on the relationship of age to the effects of losartan and hydrochlorothiazide combination in pediatric patients. Safety and efficacy have not been established. 1

Geriatrics

Studies of losartan and hydrochlorothiazide combination have included a limited number of patients 65 years of age and over. 1 No geriatrics-specific problems that would limit the usefulness of losartan and hydrochlorothiazide combination in the elderly have been identified. 1

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate) ¼ not necessarily inclusive (>> = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.

Alcohol or

Analgesics, narcotic or

Barbiturates

(concurrent administration with losartan and hydrochlorothiazide combination may potentiate orthostatic hypotension 1)

Antidiabetic agents, sulfonylurea or

Insulin

(hydrochlorothiazide may increase blood glucose concentrations; dosage adjustment of the antidiabetic medication may be necessary 1)

Anti-inflammatory drugs, nonsteroidal (NSAIDs)

(may antagonize the diuretic, natriuretic, and antihypertensive effects of hydrochlorothiazide; patients should be carefully monitored to confirm that the desired effect is being obtained 1)

Cholestyramine or

Colestipol

(cholestyramine or colstipol may inhibit gastrointestinal absorption of hydrochlorothiazide by up to 85% and 43%, respectively)

Corticosteroids

(concurrent use with hydrochlorothiazide may intensify electrolyte depletion, particularly hypokalemia 1)

Hypotension-producing medications, other (See Appendix II)

(concurrent use with losartan and hydrochlorothiazide combination may produce additive hypotensive effects 1)

>> Lithium

(concurrent use with losartan and hydrochlorothiazide combination is not recommended; hydrochlorothiazide may reduce the renal clearance of lithium and increase the risk of lithium toxicity 1)

Neuromuscular blocking agents, nondepolarizing

(hydrochlorothiazide may enhance the blockade of nondepolarizing neuromuscular blocking agents 1)

Sympathomimetics, such as norepinephrine

(losartan and hydrochlorothiazide combination may decrease the response to sympathomimetic agents; patients should be carefully monitored to confirm that the desired effect is being obtained 1)