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PHYSICIANS' DESK REFERENCE°



PHYSICIANS' PEEL REPORT

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Hydrocortone Tablets—Cont.

Ophthalmic.

Posterior subcapsular cataracts

Increased intraocular pressure

Glaucoma

Exophthalmos

Metabolic

Negative nitrogen balance due to protein catabolism Cardiovascular

Myocardial rupture following recent myocardial infarction (see WARNINGS)

Hypersensitivity

Thromboembolism Weight gain

Increased appetite Nausea

Malaise

OVERDOSAGE

Reports of acute toxicity and/or death following overdosage of glucocorticoids are rare. In the event of overdosage, no specific antidote is available; treatment is supportive and symptomatic

The intraperitoneal LD_{50} of hydrocortisone in female mice was 1740 mg/kg.

DOSAGE AND ADMINISTRATION

For oral administration
DOSAGE REQUIREMENTS ARE VARIABLE AND MUST BE INDIVIDUALIZED ON THE BASIS OF THE DISEASE

AND THE RESPONSE OF THE PATIENT.
The initial dosage varies from 20 to 240 mg a day depending on the disease being treated. In less severe diseases doses lower than 20 mg may suffice, while in severe diseases doses higher than 240 mg may be required. The initial dosage should be maintained or adjusted until the patient's response is satisfactory. If satisfactory clinical response does not occur after a reasonable period of time, discontinue HY-DROCORTONE tablets and transfer the patient to other

therapy.

After a favorable initial response, the proper maintenance dosage should be determined by decreasing the initial dosage. age in small amounts to the lowest dosage that maintains an adequate clinical response.

Patients should be observed closely for signs that might require dosage adjustment, including changes in clinical sta-tus resulting from remissions or exacerbations of the disease, individual drug responsiveness, and the effect of stress (e.g. surgery, infection, trauma). During stress it may be necessary to increase dosage temporarily.

If the drug is to be stopped after more than a few days of treatment, it usually should be withdrawn gradually.

HOW SUPPLIED

No. 7604-Tablets HYDROCORTONE, 10 mg each, are white, oval shaped compressed tablets, scored on one side, coded MSD 619, and are supplied as follows: NDC 0006-0619-68 in bottles of 100.

Shown in Product Identification Guide, page 323 7920528 Issued February 1997

HydroDIURIL® Tablets (Hydrochlorothiazide), U.S.P.

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DESCRIPTION

HydroDIURIL* (Hydrochlorothiazide) is a diuretic and antihypertensive. It is the 3,4-dihydro derivative of chlorothi-azide. Its chemical name is 6-chloro-3,4-dihydro-2*H* -1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Its empirical formula is C7H8ClN3O4S2 and its structural formula is:

It is a white, or practically white, crystalline powder with a molecular weight of 297.74, which is slightly soluble in water, but freely soluble in sodium hydroxide solution.

HydroDIURIL is supplied as 25 mg and 50 mg tablets for oral use. Each tablet contains the following inactive ingredients: calcium phosphate, FD&C Yellow 6, gelatin, lactose, magnesium stearate, starch and talc.

*Registered trademark of MERCK & CO., INC.

CLINICAL PHARMACOLOGY

The mechanism of the antihypertensive effect of thiazides is unknown. HydroDIURIL does not usually affect normal blood pressure.

HydroDIURIL affects the distal renal tubular mechanism of electrolyte reabsorption. At maximal therapeutic dosage all thiazides are approximately equal in their diuretic efficacy. HydroDIURIL increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium and bicarbonate. After oral use diuresis begins within 2 hours, peaks in about

4 hours and lasts about 6 to 12 hours.

Pharmacokinetics and Metabolism
HydroDIURIL is not metabolized but is eliminated rapidly by the kidney. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. At least 61 percent of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

INDICATIONS AND USAGE

HydroDIURIL is indicated as adjunctive therapy in edema associated with congestive heart failure, hepatic cirrhosis,

and corticosteroid and estrogen therapy.

HydroDIURIL has also been found useful in edema due to various forms of renal dysfunction such as nephrotic syndrome, acute glomerulonephritis, and chronic renal failure. HydroDIURIL is indicated in the management of hypertension either as the sole therapeutic agent or to enhance the effectiveness of other antihypertensive drugs in the more severe forms of hypertension.

Use in Pregnancy. Routine use of diuretics during normal pregnancy is inappropriate 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.

Edema during pregnancy may arise from pathologic causes or from the physiologic and mechanical consequences of pregnancy. Thiazides are indicated in pregnancy when edema is due to pathologic causes, just as they are in the absence of pregnancy (see PRECAUTIONS, Pregnancy). Dependent edema in pregnancy, resulting from restriction of venous return by the gravid uterus, is properly treated through elevation of the lower extremities and use of support stockings. Use of diuretics to lower intravascular volume in this instance is illogical and unnecessary. During normal pregnancy there is hypervolemia which is not harmful to the fetus or the mother in the absence of cardiovascular disease. However, it may be associated with edema, rarely generalized edema. If such edema causes discomfort, increased recumbency will often provide relief. Rarely this edema may cause extreme discomfort which is not relieved by rest. In these instances, a short course of diuretic therapy may provide relief and be appropriate.

CONTRAINDICATIONS

Hypersensitivity to this product or to other sulfonamide-derived drugs.

WARNINGS

Use 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.

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.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Sensitivity reactions may occur in patients with or without

a history of allergy or bronchial asthma. The possibility of exacerbation or activation of systemic luous erythematosus has been reported.

Lithium generally should not be given with diuretics (see PRECAUTIONS, *Drug Interactions*).

PRECAUTIONS

All patients receiving diuretic therapy should be observed for evidence of fluid or electrolyte imbalance: namely, 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, in-clude dryness of mouth, thirst, weakness, lethargy, drowsi-ness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and

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). Hypokalemia may be avoided or treated by use of potassium sparing diuretics or potassium supplements such as foods with a high potassium content.

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 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 sale depletion, appropriate replacement is the therapy of choice Hyperuricemia may occur or acute gout may be precipitated in certain patients receiving thiazides.

In diabetic patients dosage adjustments of insulin or or all the control of the cont

hypoglycemic agents may be required. Hyperglycemia occur with thiazide diuretics. Thus latent diabetes mellimay become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in

the post-sympathectomy patient.

If progressive renal impairment becomes evident, considerations. withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary exception of magnesium; this may result in hypomagnesemia. Thiazides may decrease urinary calcium excretion. Thiazides ides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium tabolism. 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 ass ciated with thiazide diuretic therapy.

Laboratory Tests

Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be done at appropriate

Drug Interactions

When given 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 potentia

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.

Pressor amines (e.g., norepinephrine) -possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine) -possible increased responsiveness to the muscle relaxant.

Lithium —generally should not be given with diuretics. Di-uretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with HydroDIURIL.

Non-steroidal Anti-inflammatory Drugs —In some patients. Non-servidual Anti-inflammatory Brugs—In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when HydroDIURIL and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained. effect of the diuretic is obtained.

Drug/Laboratory Test Interactions

Thiazides should be discontinued before carrying out tests for parathyroid function (see PRECAUTIONS, *General*). Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice. Hydrochlorothiazide was not genotoxic in vitro in the Ames mutagenicity assay of Salmonella typhimurium strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or in vivo in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained only in the in vitro CHO Sis-

fied concentration. Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these spe cies were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to conception and throughout gestation.

ter Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations

of hydrochlorothiazide from 43 to 1300 µg/mL, and in the

Aspergillus nidulans non-disjunction assay at an unspeci-

Pregnancy

Teratogenic Effects—Pregnancy Category B: Studies in which hydrochlorothiazide was orally administered to pregnant mice and rats during their respective periods of major organogenesis at doses up to 3000 and 1000 mg hydrochlorothiazide/kg, respectively, provided no evidence of harm to the fetus

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictice of human response, this drug should be used during pregnancy only if clearly needed.

Nonteratogenic Effects: Thiazides cross the placental bar-

rier 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.

Nursing Mothers

Thiazides are excreted in breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue hydrochlorothiazide, taking into account the importance of the drug to the mother.

Pediatric Use

There are no well-controlled clinical trials in pediatric patients. Information on dosing in this age group is supported by evidence from empiric use in pediatric patients and published literature regarding the treatment of hypertension in such patients. (See DOSAGE AND ADMINISTRATION, Infants and Children.)

ADVERSE REACTIONS

The following adverse reactions have been reported and, within each category, are listed in order of decreasing sever-

Body as a Whole: Weakness.

Cardiovascular: Hypotension including orthostatic hypotension (may be aggravated by alcohol, barbiturates, narcotics or antihypertensive drugs).

Digestive: Pancreatitis, jaundice (intrahepatic cholestatic jaundice), diarrhea, vomiting, sialadenitis, cramping, constipation, gastric irritation, nausea, anorexia.

Hematologic: Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia.

Hypersensitivity: Anaphylactic reactions, necrotizing angi-

itis (vasculitis and cutaneous vasculitis), respiratory distress including pneumonitis and pulmonary edema, photoensitivity, fever, urticaria, rash, purpura.

Metabolic: Electrolyte imbalance (see PRECAUTIONS),

hyperglycemia, glycosuria, hyperuricemia.

Musculoskeletal: Muscle spasm.

Nervous System/Psychiatric: Vertigo, paresthesias, dizziness, headache, restlessness,

Renal: Renal failure, renal dysfunction, interstitial nephritis. (See WARNINGS.)

Skin: Erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, alopecia.

Special Senses: Transient blurred vision, xanthopsia.
Urogenital: Impotence.

Whenever adverse reactions are moderate or severe, thianide dosage should be reduced or therapy withdrawn.

OVERDOSAGE

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.

In the event of overdosage, symptomatic and supportive measures should be employed. Emesis should be induced or pastric lavage performed. Correct dehydration, electrolyte balance, hepatic coma and hypotension by established procedures. If required, give oxygen or artificial respiration are respiratory impairment. The degree to which hydrochlosthiazide is removed by hemodialysis has not been estab-

The oral LD50 of hydrochlorothiazide is greater than 10 g/kg the mouse and rat.

DOSAGE AND ADMINISTRATION

Therapy should be individualized according to patient response. Use the smallest dosage necessary to achieve the required response.

For Edema

The usual adult dosage is 25 to 100 mg daily as a single or third dose. Many patients with edema respond to intermentant therapy, i.e., administration on alternate days or on ree to five days each week. With an intermittent schedule, mbalance are less likely to occur.

The Control of Hypertension usual initial dose in adults is 25 mg daily given as a and that does in datas is 20 mg daily given as a single dose. The dose may be increased to 50 mg daily, given a single or two divided doses. Doses above 50 mg are ofassociated with marked reductions in serum potassium == also PRECAUTIONS).

mients usually do not require doses in excess of 50 mg of prochlorothiazide daily when used concomitantly with mer antihypertensive agents.

Infants and Children

Diversis and For Control of Hypertension

usual pediatric dosage is 0.5 to 1 mg per pound (1 to 2

mgkg) per day in single or two divided doses, not to exceed 5 mg per day in infants up to 2 years of age or 100 mg per day in children 2 to 12 years of age. In infants less than 6 months of age, doses up to 1.5 mg per pound (3 mg/kg) per tar in two divided doses may be required. (See PRECAU-MONS, Pediatric Use.)

HOW SUPPLIED

No. 3263-Tablets HydroDIURIL, 25 mg, are peach-colored round, scored, compressed tablets, coded MSD 42 on one side and HydroDIURIL on the other. They are supplied as

NDC 0006-0042-68 bottles of 100

NDC 0006-0042-82 bottles of 1000. Shown in Product Identification Guide, page 323 No. 3264—Tablets HydroDIURIL, 50 mg, are peach-colored, round, scored, compressed tablets, coded MSD 105 on one side and HydroDIURIL on the other. They are supplied as

NDC 0006-0105-68 bottles of 100 NDC 0006-0105-86 bottles of 5000.

Shown in Product Identification Guide, page 323

Keep container tightly closed. Protect from light, moisture freezing, -20°C (-4°F) and store at room temperature, 15-

30°C (59–86°F).
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HYZAAR® 50-12.5 R (losartan potassium-hydrochlorothiazide tablets) R **HYZAAR® 100-25**

(losartan potassium-hydrochlorothiazide tablets)

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, HYZ-AAR should be discontinued as soon as possible. See WARNINGS: Fetal/Neonatal Morbidity and Mortality.

DESCRIPTION

<code>HYZAAR* 50-12.5</code> (losartan potassium-hydrochlorothia-zide) and <code>HYZAAR* 100-25</code> (losartan potassium-hydrochlorothiazide), combines an angiotensin II receptor (type $\mathrm{AT_1}$) antagonist and a diuretic, hydrochlorothiazide.

Losartan potassium, a non-peptide molecule, is chemically described as 2-butyl-4-chloro-1-[p-(o-1H-tetrazol-5-ylphenyl)benzyl]imidazole-5-methanol monopotassium salt. Its empirical formula is C22H22ClKN6O, and its structural formula is:

Losartan potassium is a white to off-white free-flowing crys talline powder with a molecular weight of 461.01. It is freely soluble in water, soluble in alcohols, and slightly soluble in common organic solvents, such as acetonitrile and methyl

Oxidation of the 5-hydroxymethyl group on the imidazole ring results in the active metabolite of losartan.

Hydrochlorothiazide is 6-chloro-3,4-dihydro-2*H*-1,2,4-benzo-thiadiazine-7-sulfonamide 1,1-dioxide. Its empirical formula is C7H8ClN3O4S2 and its structural formula is:

Hydrochlorothiazide is a white, or practically white, crystal-line powder with a molecular weight of 297.74, which is slightly soluble in water, but freely soluble in sodium hydroxide solution.

HYZAAR is available for oral administration in two tablet combinations of losartan and hydrochlorothiazide. HYZAAR 50-12.5 contains 50 mg of losartan potassium and 12.5 mg of hydrochlorothiazide. HYZAAR 100-25 contains 100 mg of losartan potassium and 25 mg of hydrochlorothiazide. Inactive ingredients are microcrystalline cellulose, lactose hydrous, pregelatinized starch, magnesium stearate, hydroxy propyl cellulose, hydroxypropyl methylcellulose, titanium dioxide and D&C yellow No. 10 aluminum lake. HYZAAR 50-12.5 contains 4.24 mg (0.108 mEq) of potas-

sium and HYZAAR 100-25 contains 8.48 mg (0.216 mEq) of

*Registered trademark of E.I. du Pont de Nemours and Company, Wilmington, Delaware, USA

CLINICAL PHARMACOLOGY

Mechanism of Action

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 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 AT₁ 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. The active metaboratory olite 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.

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 increases in plasma renin activity, increases in aldosterone secretion, increases 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.

The mechanism of the antihypertensive effect of thiazides is

unknown.

Pharmacokinetics

General

Losartan Potassium

Losartan is an orally active agent that undergoes substantial first-pass metabolism by cytochrome P450 enzymes. 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. 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 oncedaily 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 C_{\max} but has only minor effects on losartan decreases its C_{\max} but has only minor effects on losartan AUC or on the AUC of the metabolite (about 10% decreased).

Both losartan and its active metabolite are highly bound to plasma proteins, primarily albumin, with plasma free frac-tions of 1.3% and 0.2% respectively. Plasma protein binding is constant over the concentration range achieved with recommended doses. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

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 volume of distribution of losartan is about 34 liters and of the active metabolite is about 12 liters. 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. When losartan is 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 ¹⁴C-labeled losartan, about 35% of radioactivity is recovered in the urine and about 60% in the feces. Following an intravenous dose of ¹⁴C-labeled losartan, about 45% of radioactivity is recovered in the urine and 50% in the feces.

Continued on next page

Information on the Merck & Co., Inc. products listed on these pages is the full prescribing information from product circulars in use August 31, 1999. For information, please call 1-800-NSC MERCK [1-800-672-6372].