

BRIEF SUMMARY

DESCRIPTION: LOZOL (indapamide) is an oral antihypertensive/diuretic.

INDICATIONS AND USAGE: LOZOL is indicated for the treatment of hypertension, alone or in combination with other antihypertensive drugs.

LOZOL is also indicated for the treatment of salt and fluid retention associated with congestive heart failure.

Usage in Pregnancy: (see PRECAUTIONS).

Contraindications: Anuria, hypersensitivity to indapamide or other sulfonamide-derived drugs.

WARNINGS: Hypokalemia occurs commonly with diuretics, and electrolyte monitoring is essential. In general, diuretics should not be given concomitantly with lithium.

PRECAUTIONS: GENERAL: 1. *Hypokalemia and Other Fluid and Electrolyte Imbalances:* Periodic determinations of serum electrolytes should be performed at appropriate intervals. In addition, patients should be observed for clinical signs of fluid or electrolyte imbalance, such as hyponatremia, hyponatremic alkalosis, or hypokalemia. Electrolyte determinations are particularly important in patients who are vomiting excessively or receiving parenteral fluids, in patients subject to electrolyte imbalance (including those with heart failure, kidney disease, and cirrhosis), and in patients on a salt-restricted diet. The risk of hypokalemia secondary to diuresis and natriuresis is increased when larger doses are used, when the diuresis is brisk, when severe cirrhosis is present and during concomitant use of corticosteroids or ACTH. Interference with adequate oral intake of electrolytes will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis, such as increased ventricular irritability. Dilutional hyponatremia may occur in edematous patients; the appropriate treatment is restriction of water rather than administration of salt, except in rare instances when the hyponatremia is life threatening. However, in actual salt depletion, appropriate replacement is the treatment of choice. Any chloride deficit that may occur during treatment is generally mild and usually does not require specific treatment except in extraordinary circumstances as in liver or renal disease. 2. *Hyperuricemia and Gout:* Serum concentrations of uric acid increased by an average of 1.0 mg/100 ml in patients treated with indapamide, and frank gout may be precipitated in certain patients receiving indapamide (see ADVERSE REACTIONS). Serum concentrations of uric acid should therefore be monitored periodically during treatment. 3. *Renal Impairment:* Renal function tests should be performed periodically during treatment with indapamide. 4. *Impaired Hepatic Function:* Indapamide, like the 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. 5. *Glucose Tolerance:* Latent diabetes may become manifest and insulin requirements in diabetic patients may be altered during thiazide administration. Serum concentrations of glucose should be monitored routinely during treatment with indapamide. 6. *Calcium Excretion:* Calcium excretion is decreased by diuretics pharmacologically related to indapamide. Indapamide may decrease serum PBI levels without signs of thyroid disturbance. 7. *Interaction With Systemic Lupus Erythematosus:* Thiazides have exacerbated or activated systemic lupus erythematosus.

DRUG INTERACTIONS: 1. *Other Antihypertensives:* LOZOL (indapamide) may add to or potentiate the action of other antihypertensive drugs. 2. *Lithium:* See WARNINGS. 3. *Post-Sympathectomy Patient:* The antihypertensive effect of the drug may be enhanced in the post-sympathectomized patient. 4. *Norepinephrine:* Indapamide may decrease arterial responsiveness to norepinephrine, but this diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. **CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY:** Both mouse and rat life-time carcinogenicity studies were conducted. There was no significant difference in the incidence of tumors between the indapamide-treated animals and the control groups.

PREGNANCY/TERATOGENIC EFFECTS: PREGNANCY CATEGORY B. Diuretics are known to cross the placental barrier and appear in cord blood. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS: It is not known whether this drug is excreted in human milk. If use of this drug is deemed essential, the patient should stop nursing.

ADVERSE REACTIONS: Most adverse effects have been mild and transient. In long-term controlled clinical studies, dizziness to or greater than 5% cumulative adverse reactions are headache, equine, fatigue, weakness, loss of energy, lethargy, tiredness, or malaise, muscle cramps or spasms, or numbness of the extremities, nervousness, tension, anxiety, irritability, or agitation; and less than 5% cumulative adverse reactions are lightheadedness, drowsiness, vertigo, insomnia, depression, blurred vision, constipation, nausea, vomiting, diarrhea, gastric irritation, abdominal pain or cramps, anorexia, orthostatic hypotension, premature ventricular contractions, irregular heart beat, palpitations, frequency of urination, nocturia, polyuria, rash, hives, pruritus, vasculitis, impotence or reduced libido, rhinorrhea, flushing, hyperuricemia, hyperglycemia, hyponatremia, hypochloremia, increase in serum urea nitrogen (BUN) or creatinine, glycosuria, weight loss, dry mouth, tingling of extremities. Clinical hypokalemia occurred in 3% and 7% of patients given indapamide 2.5 mg and 5.0 mg, respectively.

OVERDOSAGE: Symptoms include nausea, vomiting, weakness, gastrointestinal disorders and disturbances of electrolyte balance. In severe instances, hypotension and depressed respiration may be observed. If this occurs, support of respiration and cardiac circulation should be instituted. There is no specific antidote. An evacuation of the stomach is recommended by emesis and gastric lavage after which the electrolyte and fluid balance should be evaluated carefully.

HOW SUPPLIED: White, round film-coated tablets of 2.5 mg in bottles of 100, 1,000, 2,500, and in unit-dose blister packs, boxes of 300 (10 x 10 strips).

CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.

See product circular for full prescribing information.

RORER PHARMACEUTICALS

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TOPICAL THERAPY FOR SUPERFICIAL WOUNDS

To the Editor:

I read with great interest the well-done study on the use of topical antibiotics, antiseptics, and wound protectants (*Leyden JJ, Bartelt NM: Comparison of topical antibiotic ointments, a wound protectant, and antiseptics for the treatment of human blister wounds contaminated with Staphylococcus aureus. J Fam Pract 1987; 24:601-604*). I was glad to see such good work being done in an area important to office practice.

I believe that further conclusions are in order from the data provided. On the basis of demonstration of equal efficacy and wound healing with the neomycin-polymyxin B-bacitracin ointment as compared with polymyxin B-bacitracin ointment, it would seem justifiable from a clinical standpoint to conclude that the latter ointment, which lacks the frequent topical sensitization seen with neomycin, should be used in preference to the former triple antibiotic ointment. I feel that the authors' conclusions centering around the triple antibiotic ointment gave the impression that this ointment was favored over the bacitracin-polymyxin combination. I have had excellent luck with the bacitracin-polymyxin product in clinical practice. It would seem that the data from this study would corroborate the recommendations of many dermatologists to avoid the use of topical neomycin, as equal efficacy was demonstrated in terms of actual wound healing, if not in time to sterilization of the wound.

*Robert D. Sheeler, MD
Midelfort Clinic
Eau Claire, Wisconsin*

The preceding letter was referred to Dr. Leyden, who responds as follows:

In reply to Dr. Sheeler's letter on our study comparing various topical

antimicrobial and antibiotic therapies for superficial wounds contaminated with pathogenic bacteria, I would make the following points.

1. The main thrust of our conclusions was that topical antibiotic ointments were more effective than a variety of topical antimicrobial agents in that the latter have a potential for toxicity to wounds and can delay wound healing and that topical antibiotics are more effective in suppressing *Staphylococcus aureus* and *S pyogenes*. We did not attempt to settle the issue of whether neomycin should or should not be used.

2. Neomycin is not a potent allergen and is associated with rather low levels of contact allergy when used briefly or intermittently. Prolonged use for stasis ulcers, external otitis, or chemically inflamed skin can result in increased levels of contact allergy.^{1,2}

We agree with Dr. Sheeler that the combination of bacitracin-polymyxin is a very efficacious product. The addition of neomycin can also be used safely in the appropriate clinical setting.

*James J. Leyden, MD
Department of Dermatology
University of Pennsylvania Hospital
Philadelphia*

References

- Leyden J, Kligman A: Contact dermatitis to neomycin sulfate. *JAMA* 1979; 242:1276-1278
- Prystowsky S, Nonomoura J, Smith R, Allen A: Allergic hypersensitivity to neomycin. *Dermatol* 1979; 115:713-715

ENDOCARDITIS AND MITRAL VALVE PROLAPSE

To the Editor:

The recent article by Birrer et al (*Birrer R, Mitchell K, Salvatore V: Infective endocarditis. J Fam Pract 1987; 24:289-295*) provided an excellent clinical review of endocarditis.

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Entex[®] LA

PHENYLEPHRINE HYDROCHLORIDE 75 mg
GUAIFENESIN 400 mg

IN A SPECIAL BASE TO PROVIDE A PROLONGED THERAPEUTIC EFFECT.

OR

Entex[®] LIQUID

Each 5 ml (one teaspoonful) contains:
PHENYLEPHRINE HYDROCHLORIDE 5 mg
PHENYLEPHRINE HYDROCHLORIDE 20 mg
GUAIFENESIN 100 mg
ALCOHOL 5%

Before prescribing or administering, see package circular for full product information. The following is a brief summary.

INDICATIONS AND USAGE: Entex is indicated for the symptomatic relief of sinusitis, bronchitis, pharyngitis, and coryza when these conditions are associated with nasal congestion and viscous mucus in the lower respiratory tract.

CONTRAINDICATIONS: Entex is contraindicated in individuals with known hypersensitivity to sympathomimetics, severe hypertension, or in patients receiving monoamine oxidase inhibitors.

WARNINGS: Sympathomimetic amines should be used with caution in patients with hypertension, diabetes mellitus, heart disease, peripheral vascular disease, increased intraocular pressure, hyperthyroidism, or prostatic hypertrophy.

PRECAUTIONS: Information for Patients: Do not crush or chew Entex LA tablets prior to swallowing.

Drug Interactions: Entex should not be used in patients taking monoamine oxidase inhibitors or other sympathomimetics.

Drug/Laboratory Test Interactions: Guaifenesin has been reported to interfere with clinical laboratory determinations of urinary 5-hydroxyindoleacetic acid (5-HIAA) and urinary vanilmandelic acid (VMA).

Pregnancy: Pregnancy Category C. Animal reproduction studies have not been conducted with Entex. It is also not known whether Entex can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Entex should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether the drugs in Entex are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the product, taking into account the importance of the drug to the mother.

Pediatric Use: Entex LA: Safety and effectiveness of Entex LA tablets in children below the age of 6 have not been established.

Entex Liquid: Safety and effectiveness of Entex Liquid in children below the age of 2 have not been established.

ADVERSE REACTIONS: Possible adverse reactions include nervousness, insomnia, restlessness, headache, nausea, or gastric irritation. These reactions seldom, if ever, require discontinuation of therapy. Urinary retention may occur in patients with prostatic hypertrophy.

OVERDOSAGE: The treatment of overdosage should provide symptomatic and supportive care. If the amount ingested is considered dangerous or excessive, induce vomiting with ipecac syrup unless the patient is convulsing, comatose, or has lost the gag reflex, in which case perform gastric lavage using a large-bore tube. If indicated, follow with activated charcoal and a saline cathartic. Since the effects of Entex may last up to 12 hours, treatment should be continued for at least that length of time.

DOSAGE AND ADMINISTRATION: Entex LA: Adults and children 12 years of age and older — one tablet twice daily (every 12 hours); children 6 to under 12 years — one-half (1/2) tablet twice daily (every 12 hours). Entex LA is not recommended for children under 6 years of age. Tablets may be broken in half for ease of administration without affecting release of medication but should not be crushed or chewed prior to swallowing.

Entex Liquid: All dosage should be administered four times daily (every 6 hours).

Children:
2 to under 4 years 1/2 teaspoonful (2.5 ml)
4 to under 6 years 1 teaspoonful (5.0 ml)
6 to under 12 years 1 1/2 teaspoonfuls (7.5 ml)

Adults and children 12 years of age and older:
2 teaspoonfuls (10.0 ml)

HOW SUPPLIED: Entex LA is available as a blue, scored tablet imprinted with "ENTEX LA" on the smooth side. **Entex Liquid** is available as an orange-colored, pleasant-tasting liquid.

Entex LA

NDC 0149-0436-01 bottle of 100

NDC 0149-0436-05 bottle of 500

Entex Liquid

NDC 0149-0414-16 16 FL. OZ. (1 Pint) bottle

CAUTION: Federal law prohibits dispensing without prescription.

LQ-BSS/LA-BSS

REVISED JULY 1985 (Entex LA)

REVISED SEPTEMBER 1985 (Entex Liquid)

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LETTERS TO THE EDITOR

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I believe, however, that the role of mitral valve prolapse was understated. The relative risk for mitral valve prolapse is estimated to be 4.8.¹ While the prevalence of mitral valve prolapse in the general population is 4 to 5 percent,^{1,2} this condition is present in as many as 29 percent of cases of infective endocarditis.³ With the prevalence of rheumatic heart disease declining, mitral valve prolapse will be the risk factor for infective endocarditis most often encountered by family physicians. Family physicians should become adept in making the diagnosis of mitral valve prolapse in the primary care setting so that they can identify those mitral valve prolapse patients who are at greatest risk for infective endocarditis. According to MacMahon et al, 89 percent of the risk exists in the mitral valve prolapse patients with systolic murmurs.⁴

Mark Johnson, MD
Department of Family Medicine
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References

1. MacMahon SW, Roberts JK, Kramer-Fox R, et al: Mitral valve prolapse and infective endocarditis. *Am Heart J* 1987; 113:1291-1298
2. Savage D, Garrison R, Devereux R, et al: Mitral valve prolapse in the general population. I. Epidemiologic features: The Framingham Study. *Am Heart J* 1983; 106: 571-576
3. McKinsey DS, Ratts TE, Bisno AL: Underlying cardiac lesions in adults with infective endocarditis. The changing spectrum. *Am J Med* 1987; 82:681-688
4. MacMahon SW, Hickey AJ, Wilcken DEL, et al: Risk of infective endocarditis in mitral valve prolapse with and without precordial systolic murmurs. *Am J Cardiol* 1986; 58: 105-108

FREON 12 AND VERRUCA LESIONS

To the Editor:

I am writing you in response to the many letters and telephone calls that

Mary Wester and I have received since publication of our article, "Use of Freon 12 in Treating Verruca Lesions" (*J Fam Pract* 1987; 25:73-77). I would like to state that to my knowledge dichlorodifluoromethane (Freon 12) has never been indicated, used, or distributed for use in clinical medicine prior to this time. It is currently distributed for laboratory use only by several scientific companies. I had some difficulty in obtaining the product for our clinical work.

I have recently discussed with a major packager the need for marketing Freon 12 and chlorodifluoromethane (Freon 22), which I have recently been using. We are currently working to develop a stainless steel spray nozzle for a more precise delivery of spray to the skin, and for a more professional appearance of the spray apparatus. In addition, I have found that a taller neoprene cone is needed to contain the Freon properly and prevent splattering and spillage. The manufacturer hopes to have a kit available for distribution of these items and instructional booklets within the next six months.

We are also very enthusiastic about the use of Freon 22. This is a slightly colder Freon, -41 °C boiling point vs -29 °C for Freon 12. Freon 22 has a higher vapor pressure and needs a reinforced, somewhat more expensive can for packaging and storage.

For more information regarding the successful clinical treatment of verruca lesions, actinic keratosis, seborrheic keratosis, condyloma acuminatum, and senile lentigines with the Freons, I suggest that interested physicians send their names and addresses to my address: Dr. Ronald A. McDow, 7356 Cabot Drive, Nashville, TN 37209. We will be happy to forward information later this year when the kit becomes commercially available.

Ronald A. McDow, MD
Nashville, Tennessee

HEALTH CARE IN NICARAGUA

To the Editor:

It is with interest that I read the letter to the editor by Patrick Mongan, MD, criticizing "A Report on Health Care in Nicaragua" by Drickey et al in the Family Practice Grand Rounds (*J Fam Pract* 1987; 24:349-356). He feels "that at best it disinformed us," and yet offers no specifics to counter this information. I am impressed (negatively so) with the consistency of such criticism presented by people who have not been to Nicaragua to observe the reality that nation is experiencing. *American Medical News*, in its February 13, 1987 issue, provided equal time to both sides of the argument from the physician viewpoint. Those having been to Nicaragua uniformly related specifics as to how "The Contras operate mainly by terrorizing the rural population with attacks and ambushes on small towns." Those who did not want to believe this reality suggested vague rhetoric to discount such specifics or even justify them.

My personal experience as a physician in the countryside (and war zone) of Nicaragua (August 1984 to November 1985, June to July 1987) leaves no doubt that the Contras attack primarily civilian targets and that, in fact, "health workers . . . are targeted." Such attacks occur daily and continue to be reported even as attempts are being made toward hammering out a Central American peace accord.

What impressed me most, beyond the tremendous strides made in preventive medicine, is the capability of individuals carrying out health responsibilities in the midst of such danger. Most recently I appreciated a 16-year-old male "nurse auxiliary" who worked side by side with me seeing 50 patients (each) every day. His handling of a somewhat difficult delivery, including oxytocin drip, was

phenomenal, and I was impressed with the medical school-type questions he answered along the way. I feel we have much to gain from such as "A Report on Health Care in Nicaragua" and will look forward to expansion of this concept.

R. Ed Myer, MD
Group Health Capitol Hill
Seattle, Washington

HEALTH CARE DECISIONS FOR AN INCOMPETENT PATIENT

To the Editor:

As illustrated by the Family Practice Grand Rounds case study (*Smith MA, Green LA, Ward P: Aggressive therapy in the care of the critically ill patient. J Fam Pract* 1987; 25:119-124), the proxy decision-making process can be difficult when a patient is incompetent. Nevertheless, there exists in the article an erroneous presumption that power of attorney legally empowers the holder to make health decisions for an incompetent patient.

Power of attorney¹ legally authorizes a person to facilitate the personal and financial transactions of another competent individual. As soon as that individual is deemed to be incompetent, however, the person holding power of attorney loses his or her authority to act as such. A durable power of attorney,¹ on the other hand, similarly entrusts an individual with the personal and financial considerations of another individual. The scope of this authority may be limited to health care decision making as cited in the article. In contrast with power of attorney, durable power of attorney attributes continuity of authority even when the patient becomes incompetent. As a result, the difference between the power of attorney and the durable power of attorney is semantically subtle but legally far-reaching.

If, indeed, the patient's friend actually had power of attorney (not durable power of attorney), her authority to act as a proxy decision maker terminated when the patient became incompetent. At this point, the friend could have been called on solely as a source of information on the patient's previously stated competent health care wishes without the legal agency to act as her proxy decision maker.

On the other hand, if the patient's friend had durable power of attorney, she had specific duties to fulfill. The proxy decision maker is charged with choosing the health care options that are most compatible with the patient's previously expressed written or oral directives. If no such preferences were ever elicited, a "substituted judgment,"¹ utilizing the patient's value system, determines the proxy's decision. Otherwise, if a proxy is allowed to make decisions based on his or her own value system, it would violate the medical team's attempt to preserve the patient's autonomy.

Physicians must know precisely what legal authority a potential proxy decision maker has prior to acknowledging his or her right to consent for another person. Further, the proxy's duties to carry out the patient's wishes should be clarified between the proxy and the medical team so that the patient's autonomous desires—not the proxy's—will be fulfilled.

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Reference

1. President's Commission for the Study of Ethical Programs in Medicine and Biomedical and Behavior Research: Deciding to Forego Life-Sustaining Treatment. Government Printing Office, 1983, pp 146, 147, 132-134