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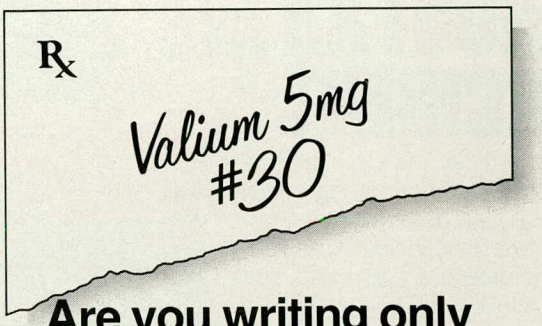
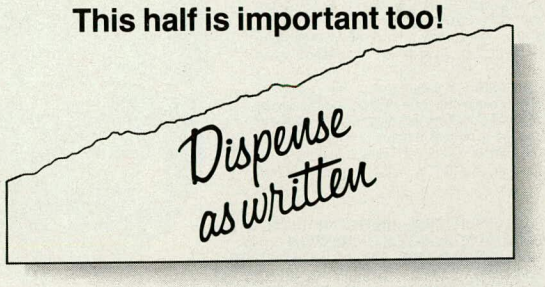
On the average, only one in 10,000 promising new compounds is ever introduced as a new product. And about $90 million is usually spent on that product before it's available for your prescription. To follow up on discoveries like Valium® (brand of diazepam/Roche), Roche is now spending, on a worldwide basis, about 20 cents of every sales dollar in up-front drug research and development. It's our way of making sure that tomorrow's drugs are available tomorrow.



Are you writing only half a prescription for it?

This half is important too!



Be sure to write a complete prescription.
Specify "Dispense as written" or
"Do not substitute" or "Medically necessary."

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VALIUM®
brand of
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2-mg 5-mg 10-mg

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ONE BILLION DIVES DOWN THE G.I. TRACT...

WITHOUT AN ACCIDENT.

In over ten years of clinical use — that's 2.6 million patient years and over one billion doses — there has been *not one* incident of small bowel ulceration reported with KAON-CL® 6.7 mEq tablets and KAON CL-10™ tablets.

KAON CL-10™
(POTASSIUM CHLORIDE)
10 mEq wax matrix, Controlled-Release Tablets

KAON-CL® (POTASSIUM CHLORIDE)
6.7 mEq wax matrix, Controlled-Release Tablets

NO SAFER WAY ON RECORD TO GET SOLID-DOSE POTASSIUM TO ITS DESTINATION

Description: KAON CL-10 is a sugar coated (not enteric-coated) tablet containing 750 mg potassium chloride (equivalent to 10 mEq potassium chloride) in a wax matrix. This formulation is intended to provide a controlled release of potassium from the matrix to minimize the likelihood of producing high localized concentrations of potassium within the gastrointestinal tract.

KAON-CL is a sugar coated (not enteric-coated) tablet containing 500 mg potassium chloride (equivalent to 6.7 mEq potassium chloride) in a wax matrix. Contains color additives including FD&C Yellow No. 5 (tartrazine). This formulation is intended to provide a controlled release of potassium from the matrix to minimize the likelihood of producing high localized concentrations of potassium within the gastrointestinal tract.

Indications:
BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUIDS OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis, in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.
2. For the prevention of potassium depletion when the dietary intake is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure; hepatic cirrhosis with ascites, states of aldosterone excess with normal renal function, potassium-losing nephropathy, and with certain diarrheal states.
3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

Contraindications: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium. Potassium supplementation, when indicated in such patients, should be with a liquid preparation.

All solid dosage forms of potassium chloride supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation.

Warnings:
Hyperkalemia — In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium Sparing Diuretics — Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal Lesions — Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. KAON-CL and KAON CL-10 are wax-matrix tablets formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient years) than with enteric-coated potassium chloride tablets (40-50 per 100,000 patient years) cases associated with wax-matrix tablets have been reported both in foreign countries and in the United States. In addition, perhaps because the wax-matrix preparations are not enteric-coated and release potassium in the stomach, there have been reports of upper gastrointestinal bleeding associated with these products. The total number of gastrointestinal lesions remains less than one per 100,000 patient years. KAON-CL and KAON CL-10 should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic Acidosis — Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.

Precautions: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

KAON-CL contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

Adverse Reactions: The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose.

The most severe adverse effects are hyperkalemia (see Contraindications, Warnings and Overdosage) and gastrointestinal obstruction, bleeding or perforation (see Warnings).

Overdosage: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see Contraindications and Warnings). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-waves, loss of P-wave, depression of S-T segment, and prolongation of the QT interval). Late manifestations include muscle-paralysis and cardiovascular collapse from cardiac arrest.

Treatment measures for hyperkalemia include the following:
1. Elimination of foods and medications containing potassium and of potassium-sparing diuretics.
2. Intravenous administration of 300 to 500 ml/hr of 10% dextrose solution containing 10-20 units of crystalline insulin per 1,000 ml.
3. Correction of acidosis, if present, with intravenous sodium bicarbonate.
4. Use of exchange resins, hemodialysis, or peritoneal dialysis.

In treating hyperkalemia, it should be recalled that in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity.

CAUTION: Federal law prohibits dispensing without prescription.

HOW SUPPLIED: KAON CL-10™ is supplied in bottles of 100 and 500; STAT-PAK® (unit dose) box of 100. KAON-CL® is supplied in bottles of 100, 250, and 1000.

Adria®
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Division of Erbamont Inc.
COLUMBUS, OHIO 43215

108505

For prevention or treatment of hypokalemia when a non-liquid potassium chloride is indicated.

There have been no reported cases of small bowel stenosis or ulceration in over ten years of clinical experience and one billion doses of KAON-CL and KAON CL-10. Reported frequency of GI lesions with wax matrix tablets is less than one per 100,000 patient years.

NOVEMBER 1986

VOLUME 86 NUMBER 11

THE JOURNAL OF THE AMERICAN OSTEOPATHIC ASSOCIATION

SPECIAL SECTION: QUALITY IN OSTEOPATHIC MEDICAL EDUCATION

ARTICLES

continued on page **703**/4

DEPARTMENTS

COVER

Radiographic and histologic evidence of interstitial pulmonary fibrosis. In the article beginning on page **735**/77, the authors suggest that their three patients may be exhibiting an incomplete form of mixed connective tissue disease, thus lending further support to an interrelationship between IPF and the collagen vascular diseases. *Cover design by Wayne and Barry Lau of Design Two, Ltd.*

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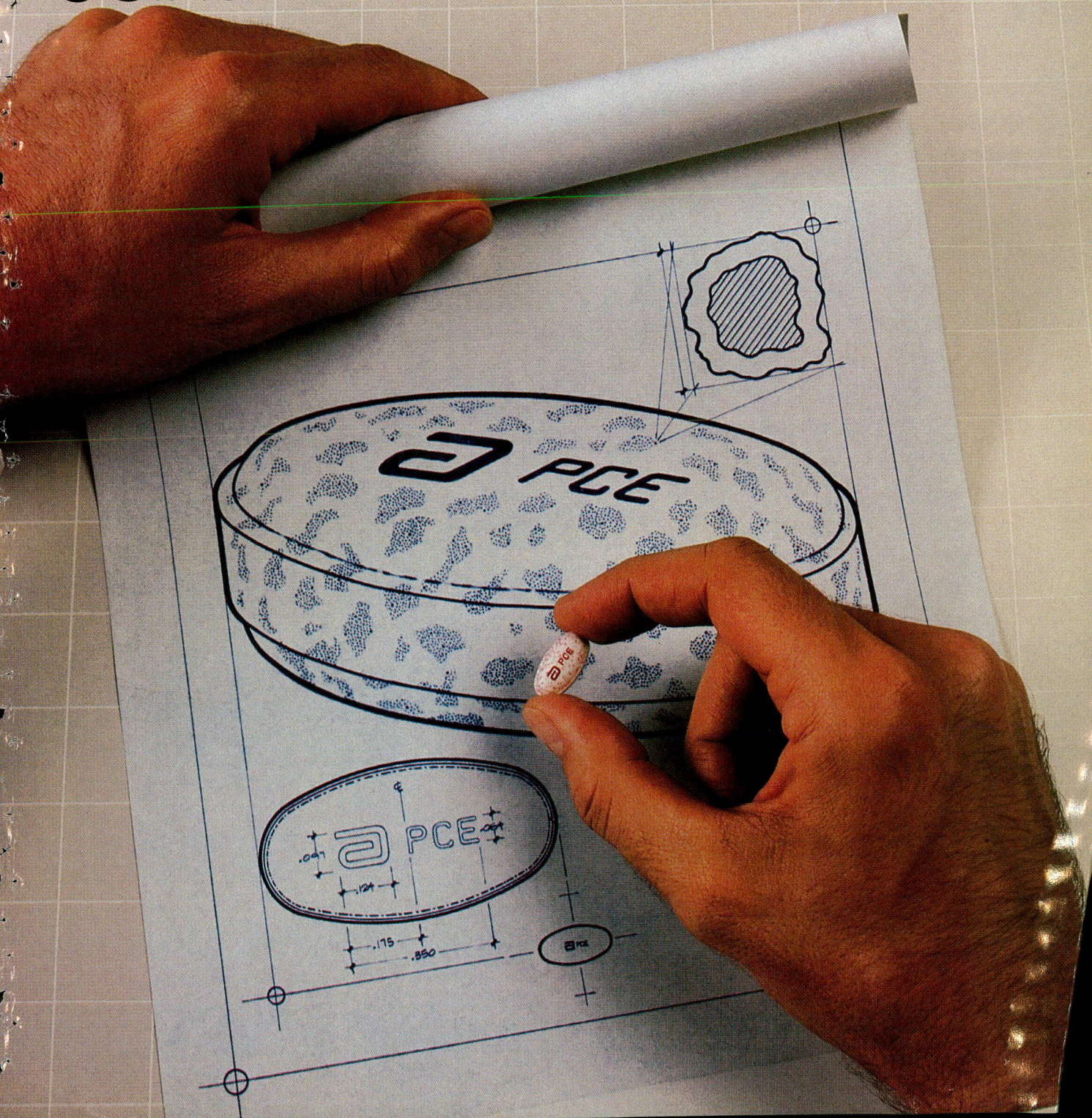
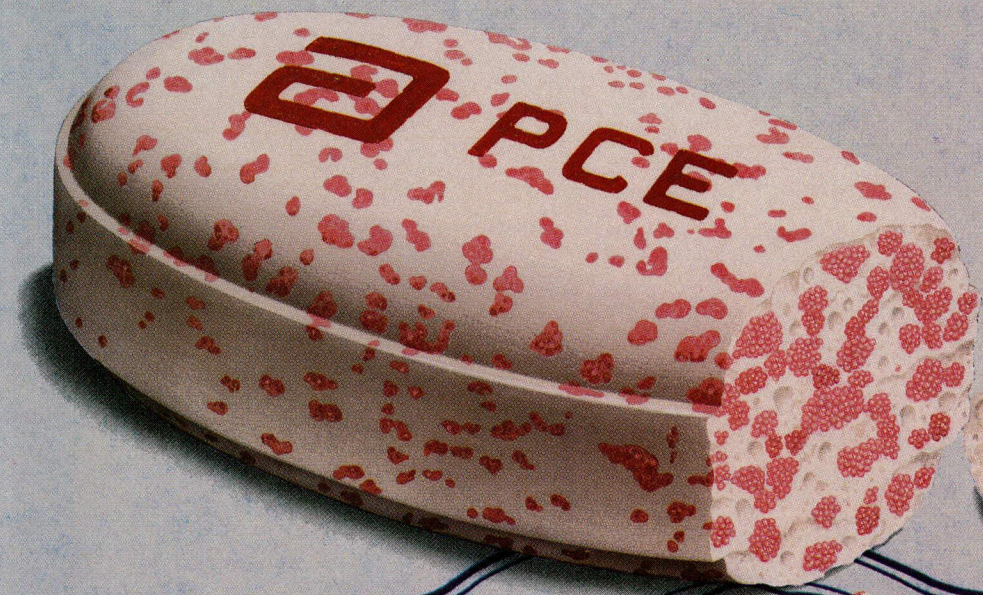
NEW

From Abbott,
an erythromycin formulation

DESIGNED FOR CONSISTENT ABSORPTION

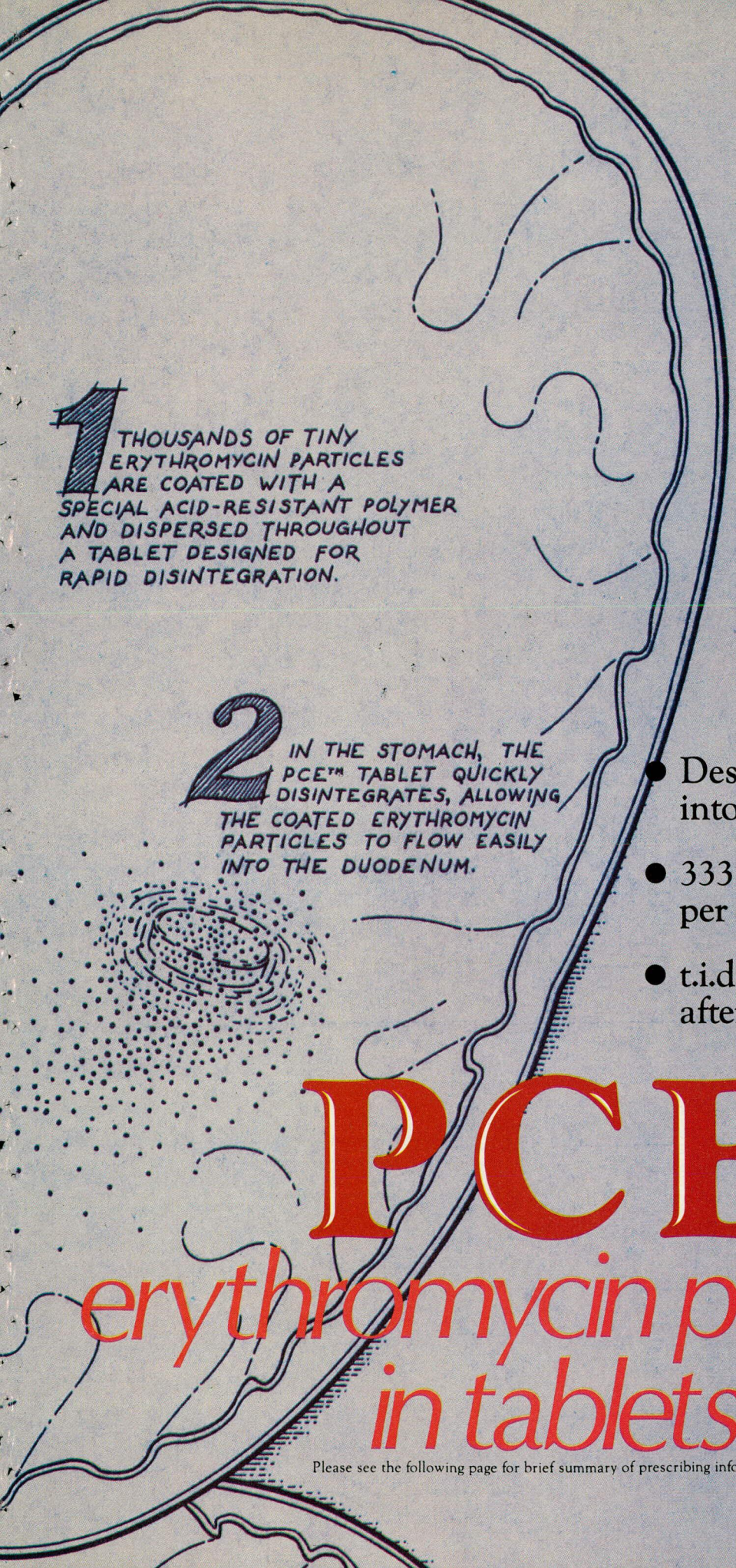


A NEW DELIVERY SYSTEM FOR CONSISTENT ABSORPTION



3

UNLIKE ENTERIC COATINGS THAT DISSOLVE LOWER IN THE GUT, THE UNIQUE PCE™ POLYMER DISSOLVES AT A pH OF 5, HIGH IN THE DUODENUM. PCE IS ABSORBED RAPIDLY AND CONSISTENTLY, IN BOTH FASTING AND NONFASTING CONDITIONS.



- Designed for minimal GI intolerance
- 333 mg of erythromycin per tablet
- t.i.d. q8h dosing; before, after, or with meals

PCE™

erythromycin particles in tablets

Please see the following page for brief summary of prescribing information.

DESIGNED FOR CONSISTENT ABSORPTION

Dose to dose, and patient to patient

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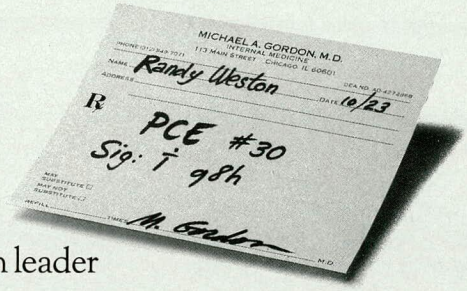
- May be given without regard to meals
- From Abbott, the worldwide erythromycin leader



NEW PCE™

erythromycin particles in tablets

Brief Summary of Prescribing Information

DESCRIPTION: PCE (erythromycin particles in tablets) Dispertab tablets are an antibacterial product containing specially coated erythromycin base particles. The coating protects the antibiotic from the inactivating effects of gastric acidity and permits efficient absorption of the antibiotic in the small intestine. Each tablet contains 333 mg of erythromycin base for oral administration.

INDICATIONS AND USAGE: PCE (erythromycin particles in tablets) is indicated in the treatment of infections caused by susceptible strains of the designated microorganisms in the diseases listed below.

Upper respiratory tract infections of mild to moderate degree caused by *Streptococcus pyogenes* (Group A beta-hemolytic streptococci); *Streptococcus pneumoniae (Diplococcus pneumoniae); Haemophilus influenzae* (when used concomitantly with adequate doses of sulfonamides, since many strains of *H. influenzae* are not susceptible to the erythromycin concentrations ordinarily achieved). (See appropriate sulfonamide labeling for prescribing information.)

Lower respiratory tract infections of mild to moderate severity caused by *Streptococcus pyogenes* (Group A beta-hemolytic streptococci): *Streptococcus pneumoniae (Diplococcus pneumoniae).*

Respiratory tract infections due to *Mycoplasma pneumoniae.*

Skin and skin structure infections of mild to moderate severity caused by *Streptococcus pyogenes* and *Staphylococcus aureus* (resistant staphylococci may emerge during treatment).

Pertussis (whooping cough) caused by *Bordetella pertussis.* Erythromycin is effective in eliminating the organism from the nasopharynx of infected individuals, rendering them noninfectious. Some clinical studies suggest that erythromycin may be helpful in the prophylaxis of pertussis in exposed susceptible individuals.

Diphtheria — As an adjunct to antitoxin in infections due to *Corynebacterium diphtheriae,* to prevent establishment of carriers and to eradicate the organism in carriers.

Erythrasma — In the treatment of infections due to *Corynebacterium minutissimum.*

Intestinal amebiasis caused by *Entamoeba histolytica* (oral erythromycins only). Extraenteric amebiasis requires treatment with other agents.

Acute pelvic inflammatory disease caused by *Neisseria gonorrhoeae:* Erythrocin® Lactobionate-I.V. (erythromycin lactobionate for injection, USP) followed by erythromycin base orally, as an alternative drug in treatment of acute pelvic inflammatory disease caused by *N. gonorrhoeae* in female patients with a history of sensitivity to penicillin. Before treatment of gonorrhea, patients who are suspected of also having syphilis should have a microscopic examination for *T. pallidum* (by immunofluorescence or darkfield) before receiving erythromycin and monthly serologic tests for a minimum of 4 months thereafter.

Erythromycins are indicated for treatment of the following infections caused by *Chlamydia trachomatis:* conjunctivitis of the newborn, pneumonia of infancy, and urogenital infections during pregnancy. When tetracyclines are contraindicated or not tolerated, erythromycin is indicated for the treatment of uncomplicated urethral, endocervical, or rectal infections in adults due to *Chlamydia trachomatis.*[1]

When tetracyclines are contraindicated or not tolerated, erythromycin is indicated for the treatment of nongonococcal urethritis caused by *Ureaplasma urealyticum.*[1]

Primary syphilis caused by *Treponema pallidum.* Erythromycin (oral forms only) is an alternative choice of treatment for primary syphilis in patients allergic to the penicillins. In treatment of primary syphilis, spinal fluid should be examined before treatment and as part of the follow-up after therapy.

Legionnaires' Disease caused by *Legionella pneumophila.* Although no controlled clinical efficacy studies have been conducted, *in vitro* and limited preliminary clinical data suggest that erythromycin may be effective in treating Legionnaires' Disease.

Prevention of Initial Attacks of Rheumatic Fever — Penicillin is considered by the American Heart Association to be the drug of choice in the prevention of initial attacks of rheumatic fever (treatment of Group A beta-hemolytic streptococcal infections of the upper respiratory tract e.g., tonsillitis, or pharyngitis).[2] Erythromycin is indicated for the treatment of penicillin-allergic patients. The therapeutic dose should be administered for ten days.

Prevention of Recurrent Attacks of Rheumatic Fever — Penicillin or sulfonamides are considered by the American Heart Association to be the drugs of choice in the prevention of recurrent attacks of rheumatic fever. In patients who are allergic to penicillin and sulfonamides, oral erythromycin is recommended by the American Heart Association in the long-term prophylaxis of streptococcal pharyngitis (for the prevention of recurrent attacks of rheumatic fever).[2]

Prevention of Bacterial Endocarditis — Although no controlled clinical efficacy trials have been conducted, oral erythromycin has been recommended by the American Heart Association for prevention of bacterial endocarditis in penicillin-allergic patients with prosthetic cardiac valves, most congenital cardiac malformations, surgically constructed systemic pulmonary shunts, rheumatic or other acquired valvular dysfunction, idiopathic hypertrophic subaortic stenosis (IHSS), previous history of bacterial endocarditis and mitral valve prolapse with insufficiency when they undergo dental procedures and surgical procedures of the upper respiratory tract.[3]

CONTRAINDICATIONS: Erythromycin is contraindicated in patients with known hypersensitivity to this antibiotic.

WARNINGS: There have been reports of hepatic dysfunction with or without jaundice, occurring in patients receiving oral erythromycin products.

PRECAUTIONS: *General:* Erythromycin is principally excreted by the liver. Caution should be exercised when erythromycin is administered to patients with impaired hepatic function. (See "Warnings" section.)

Prolonged or repeated use of erythromycin may result in an overgrowth of nonsusceptible bacteria or fungi. If superinfection occurs, erythromycin should be discontinued and appropriate therapy instituted.

When indicated, incision and drainage or other surgical procedures should be performed in conjunction with antibiotic therapy.

Laboratory Tests: Erythromycin interferes with the fluorometric determination of urinary catecholamines.

Drug Interactions: Erythromycin use in patients who are receiving high doses of theophylline may be associated with an increase of serum theophylline levels and potential theophylline toxicity. Serum theophylline levels should be monitored in patients receiving concomitant erythromycin. The theophylline dose may need to be reduced in some patients.

Erythromycin administration in patients receiving carbamazepine has been reported to cause increased serum levels of carbamazepine with subsequent development of signs of carbamazepine toxicity.

Concomitant administration of erythromycin and digoxin has been reported to result in elevated digoxin serum levels.

There have been reports of increased anticoagulant effects when erythromycin and oral anticoagulants were used concomitantly.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term (2-year) oral studies conducted in rats with erythromycin base did not provide evidence of tumorigenicity. Mutagenicity studies have not been conducted. There was no apparent effect on male or female fertility in rats fed erythromycin (base) at levels up to 0.25 percent of diet.

Pregnancy: Pregnancy Category B: There is no evidence of teratogenicity or any other adverse effect on reproduction in female rats fed erythromycin base (up to 0.25 percent of diet) prior to and during mating, during gestation, and through weaning of two successive litters. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Erythromycin has been reported to cross the placental barrier in humans, but fetal plasma levels are generally low.

Labor and Delivery: The effect of erythromycin on labor and delivery is unknown.

Nursing Mothers: Erythromycin is excreted in breast milk, therefore, caution should be exercised when erythromycin is administered to a nursing woman.

Pediatric Use: See "Indications and Usage" section.

ADVERSE REACTIONS: The most frequent side effects of oral erythromycin preparations are gastrointestinal and are dose-related. They include nausea, vomiting, abdominal pain, diarrhea and anorexia. Symptoms of hepatic dysfunction and/or abnormal liver function test results may occur (see "Warnings" section). Pseudomembranous colitis has been rarely reported in association with erythromycin therapy.

Allergic reactions ranging from urticaria and mild skin eruptions to anaphylaxis have occurred.

There have been isolated reports of reversible hearing loss occurring chiefly in patients with renal insufficiency and in patients receiving high doses of erythromycin.

OVERDOSAGE: In case of overdosage, erythromycin should be discontinued. Overdosage should be handled with the prompt elimination of unabsorbed drug and all other appropriate measures.

Erythromycin is not removed by peritoneal dialysis or hemodialysis.

REFERENCES

1. CDC Sexually Transmitted Diseases Treatment Guidelines 1985.
2. Committee on Rheumatic Fever and Infective Endocarditis of the Council on Cardiovascular Disease of the Young: Prevention of Rheumatic Fever, *Circulation* 70(6): 1118A-1122A, December 1984.
3. Committee on Rheumatic Fever and Infective Endocarditis of the Council on Cardiovascular Disease of the Young: Prevention of Bacterial Endocarditis, *Circulation* 70(6):1123A-1127A, December 1984.

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