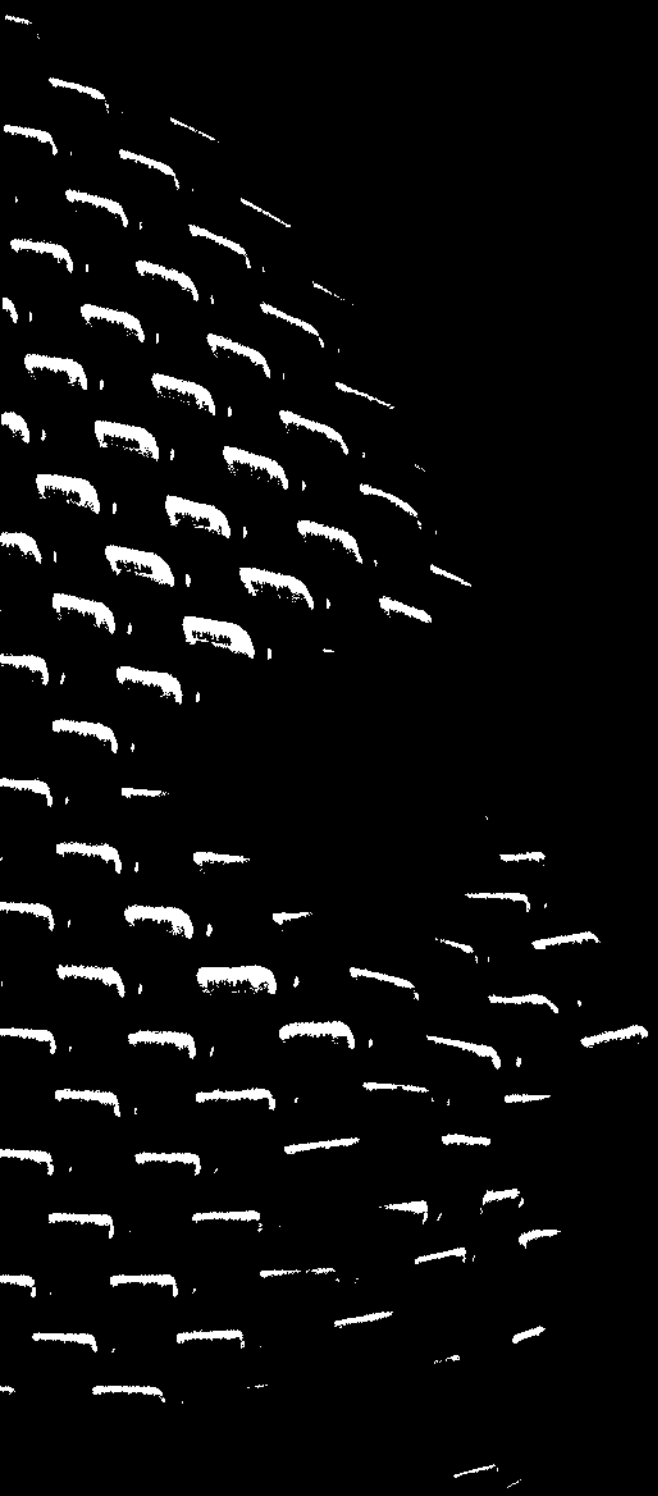
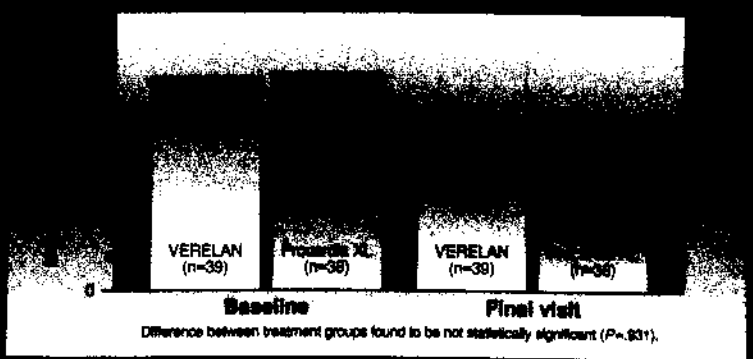


VERELAN

AS EFFECTIVE AS PROCARDIA XL® IN REDUCING BP AT THE 24TH HOUR[1,2]

Reduction in mean DBP measured 24 ± 2 hours after dosing



Results of a 12 week, randomized, double blind, parallel, comparative study of patients with mild to moderate hypertension in 10 study sites nationwide. Patients not controlled on VERELAN 240 mg/day were titrated to 360 mg/day and, if needed, 480 mg/day; patients not controlled on Procardia XL 30 mg/day were titrated to 60 mg/day and, if needed, 90 mg/day.

No significant difference between groups in the number of titrations to goal DBP (~ 90 mm Hg)

*Procardia XL is a registered trademark of Pfizer Inc.

Constipation, which can easily be managed in most patients, is the most frequently reported side effect of verapamil.

Please see brief summary of Prescribing Information including CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS on last page.

VERELAN

EXCELLENT TOLERABILITY SIMILAR TO PLACEBO IN A DOUBLE-BLIND STUDY[1,2]

Incidence of side effects commonly associated with calcium channel blockers

Results of a 4-week, double-blind, placebo-controlled study of patients with essential hypertension. VERELAN [illegible]

No patients discontinued VERELAN therapy due to constipation, headache, dizziness, or edema

ONCE-A-DAY

VERELAN®

Verapamil HCl 120 mg 180 mg 240 mg

PELLET-FILLED CAPSULES

References: 1. Levy B, Rosenberg LN, Colasante DA. A comparison of VERELAN® and Procardia® XL in the treatment of patients with mild to moderate hypertension. American College of Clinical Pharmacology. 21st Annual Meeting, 1992. Abstract. 2. Further analysis of Levy B, et al. (See reference 1.) Data on file. Lederle Laboratories, Pearl River, NY. 3. Carr AA, Bottini PB, Prisant LM, et al. Once-daily verapamil in the treatment of mild-to-moderate hypertension: a double-blind placebo-controlled dose-ranging study. *J Clin Pharmacol*. 1991;31:144-150,490. 4. Further analysis of Carr AA, et al. (See reference 3.) Data on file. Lederle Laboratories, Pearl River, NY. 5. VERELAN Prescribing Information. 6. *Physicians' Desk Reference®*. 46th ed. Montvale, NJ: Medical Economics Data; 1992:1181-1183 (Isoptin® SR) 2157-2159 (Calan® SR)

Brief Summary

VERELAN®
Verapamil HCl
Sustained-Release Pellet-Filled Capsules

For complete Prescribing Information, consult package insert.

CLINICAL PHARMACOLOGY

Food does not affect the extent or rate of the absorption of verapamil from the controlled release VERELAN capsule.

Atrioventricular block can occur in patients without preexisting condition defects (see **WARNINGS**).

Acceleration of ventricular rate and/or ventricular fibrillation has been reported in patients with atrial flutter or atrial fibrillation and a coexisting accessory AV pathway following administration of verapamil (see **WARNINGS**).

In patients with hepatic insufficiency, metabolism is delayed and elimination half-life prolonged up to 14 to 16 hours (see **PRECAUTIONS**), the volume of distribution is increased and plasma clearance reduced to about 30% of normal.

CONTRAINDICATIONS

Severe LV dysfunction (see **WARNINGS**), hypotension (systolic pressure <90 mmHg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), second- or third-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes) (see **WARNINGS**), hypersensitivity to verapamil.

WARNINGS

Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction <30%) or moderate-to-severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta blocker. Control milder heart failure with optimum digitalization and/or diuretics before VERELAN is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported.

Several cases of hepatocellular injury have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving IV verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (second- or third-degree, 0.8%). Development of marked first-degree block or progression to second- or third-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, second-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

PRECAUTIONS

Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol clearance may occur with combined use. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Verapamil has been given concomitantly with short- and long-acting nitrates without any undesirable drug interactions. Interaction between cimetidine and chronically administered verapamil has not been studied. In healthy volunteers, clearance of verapamil was reduced or unchanged. Concomitant use of lithium and verapamil may result in a lowering of serum lithium levels or increased sensitivity to lithium. Patients receiving both drugs must be monitored carefully.

Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporine. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. **Pregnancy Category C:** There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use. Safety and efficacy of verapamil in children below the age of 18 years have not been established.

ADVERSE REACTIONS

Reversible (upon discontinuation of verapamil) nonobstructive, paralytic ileus has been infrequently reported in association with the use of verapamil.

In clinical trials with 285 hypertensive patients on VERELAN for more than 1 week, the following adverse reactions were reported: constipation (7.4%); headache (6.3%); dizziness (4.2%); lethargy (3.2%), dyspepsia (2.5%); rash (1.4%); ankle edema (1.4%); sleep disturbance (1.4%); myalgia (1.1%). In clinical trials of other formulations of verapamil HCl (N = 4,954), the following reactions have occurred at rates greater than 1.0%: constipation (7.3%); dizziness (3.3%); nausea (2.7%); hypotension (2.5%); edema (1.9%); headache (2.2%), rash (1.2%); CHF/pulmonary edema (1.8%); fatigue (1.7%); bradycardia (HR<50/min) (1.4%). AV block-total 1°, 2°, 3° (1.2%); 2° and 3° (0.8%); flushing (0.5%); elevated liver enzymes (see **WARNINGS**).

The following reactions, reported in 1.0% or less of patients, occurred under conditions (open trials, marketing experience) where a causal relationship is uncertain. **Cardiovascular:** angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope **Digestive System:** diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia. **Hemic and Lymphatic:** ecchymosis or bruising. **Nervous System:** cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence. **Respiratory:** dyspnea. **Skin:** arthralgia and rash, exanthema, hair loss, hyperkeratosis, maculae, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme. **Special Senses:** blurred vision. **Urogenital:** gynecomastia, impotence, increased urination, spotty menstruation.

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Official Publication of
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Morrow JD, Margolies GR, Rowland J, Roberts LJ 2nd. Evidence that histamine is the causative toxin of scombroid-fish poisoning. N Engl J Med 1991; 324:716-20.

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Clinical Experience Network (CEN). A large-scale, office-based study evaluates the use of a new class of nonsedating antihistamines. A report from CEN. J Am Board Fam Pract 1990; 3:241-58.

Book

Rakel RE. Textbook of family practice. 4th ed. Philadelphia: WB Saunders, 1990.

Chapter in Book

Haynes RC Jr. Agents affecting calcification: calcium, parathyroid hormone, calcitonin, vitamin D, and other compounds. In: Gilman AG, Rall TW, Nies AS, Taylor P, editors. Goodman and Gilman's the pharmacological basis of therapeutics. 8th ed. New York: Pergamon Press, 1990.

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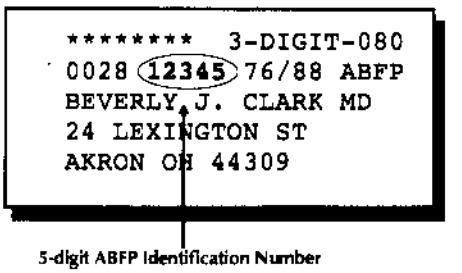

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Untie the knot of tension headache

Extra Strength **Esgic*plus*™ TABLETS**

Butalbital 50mg (Warning: May be habit forming)/Acetaminophen 500mg/Caffeine 40mg

Few complications-no aspirin-related side effects[1]
More analgesic power for fast acting relief
Convenience of a nonscheduled* analgesic

Analgesic power patients need... gentleness they deserve.

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Please see brief summary of full prescribing information on adjacent page.

*In m[illegible]

References: 1. Laska EM, Sunshine A, Meller F, et al. Caffeine as an analgesic adjuvant. *JAMA*. 1984; 251:1711-18. 2. Benson GD. Hepatotoxicity following the therapeutic use of antipyretic analgesics. *Am J Med*. 1983; 75(suppl 5A):85-93. 3. Jick H. Effects of aspirin and acetaminophen in gastrointestinal hemorrhage. *Arch Intern Med*. 1981; 141:316-321. 4. Mielke CH Jr. Comparative effects of aspirin and acetaminophen on hemostasis. *Arch Intern Med*. 1981; 305-310. 5. Hansten PD. *Drug Interactions*, ed. 5. Philadelphia: Lea & Febiger, 1985, p. 95.

ESGIC-PLUS™

Tablets (Butalbital, Acetaminophen and Caffeine Tablets, USP)
50mg/500mg/40mg

Brief Prescribing Information: (Please see package insert for full prescribing information)

DESCRIPTION: Each ESGIC-PLUS™ tablet for oral administration contains:

Butalbital*	50 mg
Acetaminophen	500 mg
Caffeine	40 mg

*WARNING: May be habit forming

CLINICAL PHARMACOLOGY: Pharmacologically, ESGIC-PLUS™ combines the analgesic properties of acetaminophen-caffeine with the anxiolytic and muscle relaxant properties of butalbital.

CONTRAINDICATIONS: Hypersensitivity to acetaminophen, caffeine, or barbiturates. Patients with porphyria.

PRECAUTIONS: General: Barbiturates should be administered with caution, if at all, to patients who are mentally depressed, have suicidal tendencies, or a history of drug abuse.

Elderly or debilitated patients may react to barbiturates with marked excitement, depression, and confusion. In some persons, barbiturates repeatedly produce excitement rather than depression.

Drug Interactions: Patients receiving narcotic analgesics, antipsychotics, anti-anxiety agents, or other CNS depressants (including alcohol) concomitantly with ESGIC-PLUS™ (Butalbital, Acetaminophen, and Caffeine) may exhibit additive CNS depressant effects.

Drugs	Effect
Butalbital with coumarin anticoagulants	Decreased effect of anticoagulant because of increased metabolism resulting from enzyme induction
Butalbital with tricyclic antidepressants	Decreased blood levels of the antidepressant.

Usage in Pregnancy: Adequate studies have not been performed in animals to determine whether this drug affects fertility in males or females, has teratogenic potential or has other adverse effects on the fetus. There are no well-controlled studies in pregnant women. Although there is no clearly defined risk, one cannot exclude the possibility of infrequent or subtle damage to the human fetus. ESGIC PLUS™ should be used in pregnant women only when clearly needed.

Nursing Mothers: The effects of ESGIC-PLUS™ on infants of nursing mothers are not known. Barbiturates are excreted in the breast milk of nursing mothers. The serum levels in infants are believed to be insignificant with therapeutic doses.

Pediatric Use: Safety and effectiveness in children below the age of 12 have not been established.

ADVERSE REACTIONS: The most frequent adverse reactions are drowsiness and dizziness. Less frequent adverse reactions are lightheadedness and gastrointestinal disturbances including nausea, vomiting and flatulence. Mental confusion or depression can occur due to intolerance or overdosage of butalbital.

Several cases of dermatological reactions including toxic epidermal necrolysis and erythema multiforme have been reported.

DRUG ABUSE & DEPENDENCE: Prolonged use of barbiturates can produce drug dependence, characterized by psychic dependence and tolerance. The abuse liability of ESGIC-PLUS™ is similar to that of other barbiturate-containing drug combinations. Caution should be exercised when prescribing medication for patients with a known propensity for taking excessive quantities of drugs, which is not uncommon in patients with chronic tension headache.

OVERDOSAGE: The toxic effects of acute overdosage of ESGIC-PLUS™ are attributable mainly to its barbiturate component, and, to a lesser extent, acetaminophen. Because toxic effects of caffeine occur in very high dosages only the possibility of significant caffeine toxicity from ESGIC-PLUS™ overdosage is unlikely.

Barbiturate: Signs and Symptoms: Drowsiness, confusion, coma; respiratory depression, hypotension; shock.

Treatment

1. Maintenance of an adequate airway, with assisted respiration and oxygen administration as necessary.
2. Monitoring of vital signs and fluid balance.
3. If the patient is conscious and has not lost the gag reflex, emesis may be induced with ipecac. Care should be taken to prevent pulmonary aspiration of vomitus. After completion of vomiting, 30 grams of activated charcoal in a glass of water may be administered.
4. If emesis is contraindicated, gastric lavage may be performed with a cuffed endotracheal tube in place with the patient in the facedown position. Activated charcoal may be left in the emptied stomach and a saline cathartic administered.
5. Fluid therapy and other standard treatment for shock, if needed.
6. If renal function is normal, forced diuresis may aid in the elimination of the barbiturate. Alkalinization of the urine increases renal excretion of some barbiturates, especially phenobarbital.
7. Although not recommended as a routine procedure, hemodialysis may be used in severe barbiturate intoxication or if the patient is anuric or in shock.

Acetaminophen: Signs and Symptoms: In acute acetaminophen overdosage, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and thrombocytopenia may also occur.

In adults, hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams and fatalities with less than 15 grams. Importantly, young children seem to be more resistant than adults to the hepatotoxic effect of an acetaminophen overdose.

Early symptoms following a potentially hepatotoxic overdosage may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may be apparent until 48 to 72 hours post-ingestion.

Treatment: The stomach should be emptied promptly by lavage or by induction of emesis with syrup of ipecac. Patients' estimates of the quantity of a drug ingested are notoriously unreliable. Therefore, if an acetaminophen overdose is suspected, a serum acetaminophen assay should be obtained as early as possible, but no sooner than four hours following ingestion. Liver function studies should be obtained initially and repeated at 24-hour intervals.

The antidote, N-acetylcysteine, should be administered as early as possible, preferably within 16 hours of the overdose ingestion for optimal results, but in any case, within 24 hours. Following recovery, there are no residual, structural or functional hepatic abnormalities.

DOSAGE AND ADMINISTRATION: Oral: One ESGIC-PLUS™ tablet every four hours as needed. Do not exceed six tablets or capsules per day.

HOW SUPPLIED: ESGIC-PLUS™ (Butalbital* 50 mg [*WARNING—May be habit forming], Acetaminophen 500 mg and Caffeine 40 mg) Tablets are white, capsule-shaped, single-scored, and are debossed "FOREST" on the upper side, "678" on one side of the score on the lower side. They are supplied as: Bottles of 100—NDC 0456-0678-01.

Storage: Store at controlled room temperature 15°-30°C (59°-86°F). Protect from moisture.

Dispense in a tight, light resistant container with a child-resistant closure.

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured by: MIKART, INC., Atlanta, GA 30318

Distributed by: FOREST PHARMACEUTICALS, INC., Subsidiary of Forest Laboratories, Inc., St. Louis, MO 63043

Revised 10-91 Code 374A00

Printed in U.S.A. ESP433