A Little Means A Lot To The Older Hypertensive

Comparable antihypertensive efficacy to 2.5 mg* with the safety profile of a lower once-daily dose

Favorable metabolic profile—no adverse effect on lipids; only 2% incidence of clinical hypokalemia

Safe and effective for step-down therapy

Side-effect profile compatible with other antihypertensive agents

LOZOL 1.25 mg once daily is now the recommended starting dose for indapamide in hypertension

LOW-DOSE 1.25 MG
ONCE-DAILY
INDAPAMIDE TABLETS

LOZOL® (indapamide) 1.25 mg, and 2.5 mg tablets

BRIEF SUMMARY

INDICATIONS: LOZOL, indapamide is indicated for the treatment of hypertension in combination with other antihypertensive drugs, and for the treatment of salt and fluid retention associated with congestive heart failure.

CONTRAINDICATIONS: Anuria, hyperosmolarity to indapamide or other sulfonamide-derived drugs.

WARNINGS: Infrequent cases of severe hyperkalemia accompanied by hypertension, have been reported with 1.25 mg and 2.5 mg daily doses in patients with severe renal insufficiency or oliguria, and in patients with congestive heart failure. In addition, patients should be observed for clinical signs of fluid or electrolyte imbalance, such as hypertension, hypotensive, or hypokalemic. The risk of hyperkalemia is increased in patients with severe renal insufficiency, in patients on a saline-restricted diet, and in patients with hyperparathyroidism. Serum concentrations of potassium should be monitored periodically.

PRECAUTIONS: Perform serum electrolyte determinations at appropriate intervals, especially in patients who are vomiting excessively or receiving parenteral fluids, in patients subject to electrolyte imbalance, or in patients on a saline-restricted diet. In addition, patients should be observed for clinical signs of fluid or electrolyte imbalance, such as hypertension, hypotensive, or hypokalemic. The risk of hyperkalemia is increased in patients with severe renal insufficiency, in patients on a saline-restricted diet, and in patients with hyperparathyroidism. Serum concentrations of potassium should be monitored periodically.

DRUG INTERACTIONS: Indapamide may add to or potentiates the action of other nephrotoxic drugs. The antihypertensive effect of the drug may be enhanced in the presence of other hypertensive agents and/or digitalis. The risk of hyperkalemia is increased in patients with severe renal insufficiency, in patients on a saline-restricted diet, and in patients with hyperparathyroidism. Serum concentrations of potassium should be monitored periodically.


Avoid excess heat. Do not use in patients with renal impairment. See package for full prescribing information.
Imagine a long, complex form required to report adverse events. Not anymore.

1-800-FDA-1088.

If it's serious, we need to know.
Living in Medicine

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LaVina Jean Armstrong

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Karen H. Calhoun, MD

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IN HYPERTENSION
OR ANGINA
IN HYPERTENSION OR ANGINA

CARDIZEM® CD
(diltiazem HCl)

FOR EFFECTIVE
24-HOUR CONTROL

ONCE A DAY
HEMODYNAMIC EFFECTS

In hypertension

- The magnitude of blood pressure reduction is related to the degree of hypertension
- Low incidence of vasodilatory side effects
- No reflex tachycardia is associated with chronic antihypertensive effects

In angina

- Potent dilator of coronary arteries* and reduces vasospasm
- Appropriate decrease in heart rate with a low incidence (<1%) of reflex tachycardia
- Little or no negative inotropic effect in patients with normal ventricular function†

WELL-TOLERATED CONTROL REGARDLESS OF AGE OR GENDER‡

- A side-effect discontinuation rate comparable to placebo in both hypertension and angina trials²
- Most commonly reported side effects are headache (5.4%), bradycardia (3.3%), first-degree AV block (3.3%), dizziness (3.0%), edema (2.6%), ECG abnormality (1.6%), and asthenia (1.8%)†

* Demonstrated in patients with vasospastic angina.
† See Warnings and Clinical Pharmacology sections in prescribing information.
‡ In clinical trials with Cardizem CD.

Please see brief summary of prescribing information on next page.
Cardinexone, Metagonism, Impairment of Fertility

A 24-month study in rats at oral dosage levels of up to 100 mg/kg/day and a 2-month study in mice at oral dosage levels of up to 30 mg/kg/day showed no evidence of carcinogenicity. There was also no mutagenic response in vitro or in vivo in mammalian cell assays or in vitro in bacteria. No evidence of impaired fertility was observed in a study performed in male and female rats at oral dosage levels of up to 100 mg/kg/day.

Pregnancy

Category C: Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the peri- and postnatal studies, there was an increased incidence of stillbirths at doses of 30 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use of Cardinexone in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Cardinexone is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of Cardinexone is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

The following table presents the most common adverse reactions reported in placebo-controlled angina and hypertension trials in patients receiving Cardinexone CD up to 390 mg with rates in placebo patients often shown for comparison.

<table>
<thead>
<tr>
<th>Adverse Reaction (n=607)</th>
<th>Placebo (n=301)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>5.4%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3.0%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3.3%</td>
</tr>
<tr>
<td>AV Block First Degree</td>
<td>3.3%</td>
</tr>
<tr>
<td>Edema</td>
<td>2.6%</td>
</tr>
<tr>
<td>ECG Abnormality</td>
<td>1.6%</td>
</tr>
</tbody>
</table>

In clinical trials of Cardinexone CD capsules, Cardinexone tablets, and Cardinexone SR capsules involving 3290 patients, the most common events (in greater than 1%) were edema (4.6%), headache (4.6%), dizziness (3.3%), asthenia (2.8%), first-degree AV block (2.4%), bradycardia (1.7%), flushing (1.4%), nausea (1.4%), and rash (1.1%).

In the following studies, the most important reactions occurring in less than 1% in angina or hypertension trials included the following:

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo (n=301)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal: nausea</td>
<td>1.0%</td>
</tr>
<tr>
<td>Gastrointestinal: vomiting</td>
<td>1.0%</td>
</tr>
<tr>
<td>Gastrointestinal: diarrhea</td>
<td>1.0%</td>
</tr>
</tbody>
</table>

References:
1. Cardinexone CD prescribing information.
2. Data on file, Marion Merrell Dow Inc.
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Stress: The Profession, the Family and You

International Conference on Physician Health September 16-20, 1994
Ottawa Westin Hotel
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Sponsored by the American Medical Association, the Canadian Medical Association, the Federation of State Medical Boards, and the Federation of Medical Licensing Authorities of Canada.

Health related problems are on our minds and in our news, affecting the way we live, the way we interact, the way we plan for our futures. They contribute to the amount of stress we face during the course of a normal day.

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Roy W. Menninger, MD, Chairman of Trustees, Menninger Foundation speaking on the general conference theme from the US perspective, and
Michael F. Myers, MD, Department of Psychiatry, University of British Columbia speaking on the general conference theme from the Canadian perspective.

Other Speakers will include:
Erica Frank, MD, on the Women Physicians Health Study
Joseph Neumman, MD, on Disability due to Illness
James Winn, MD, on Physician Health and Medical Licensing Boards

While you explore the issues, take advantage of the Ottawa Westin Hotel’s location for a personal health break. Ottawa is Canada’s capital and offers many national museums, over 60 miles of bicycle paths, and hiking in Gatineau Park and along the Rideau Canal.

For additional information on how to register for this important Conference, write or call: International Conference on Physician Health, American Medical Association, 515 N. State Street, Chicago, IL 60610. Telephone: 800 621-8335.

American Medical Association
Physicians Health Foundation
Caring for the Caregiver

Calan® SR (verapamil hydrochloride)

BRIEF SUMMARY
Contraindications: Severe LV dysfunction (see Warnings), hypertension (systolic pressure < 90 mm Hg or diastolic > 130), significant AV block (if no pacemaker is present), 2nd or 3rd degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (e.g. WPW or LGL syndromes), hypersensitivity to verapamil

Warnings: Verapamil should be avoided in patients with severe LV dysfunction, or an 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 Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes may be reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with phe- nobarbital and/or chronic atrial flutter/fibrillation and an accessory AV pathway (e.g. WPW or LGL syndromes) have developed an increased isoprenal 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 contra-indicated in such patients. AV block may occur (2nd and 3rd degree, 0.8%). Development of marked 1st degree block or progression to 2nd or 3rd degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd degree A-V block, sinus arrest, pulmonary edema and/or sphygmographic hypotension 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 use 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 Du- chenne’s muscular dystrophy and may prolong recovery in the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with atreatheptic blockers and verapamil may result in additive neuromuscular blockade. Combined treatment with beta-adrenergic blockers and verapamil may result in additive negative inotropic effects on heart rate, ventricular conduction, or cardiac contractility, there have been reports of excessive bradycardia and A-V 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 mortality and programmatic clearance may occur when either drug is administered concomitantly with verapamil. A variable effect has been seen with IV verapamil or use of oral verapamil. Chronic Verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and incremental clearance of digoxin. 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. Digoxin and verapamil 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 ver- apamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Concentration of lithium and verapamil may result in an increased sensitivity to lithium (neurotoxicity), with either no change or an increase in lithium levels. However, it may also result in a lowering of serum lithium levels. Patients receiving both drugs must be monitored carefully.

Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may decrease verapamil clearance. Verapamil may increase serum levels of cyclosporin. Verapamil may inhibit the clearance and increase the plasma levels of theophyl- line. Concomitant use of methotrexate and calcium antagonists needs careful titration to avoid excessive cardio- vascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing), dosage reduction may be required. There was no evidence of a cardiogenic potential of verapamil administered to rats for 2 years. A study in rats did not suggest a tumorigenic potential, and verapamil is 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 only if clearly needed. Verapamil is excreted in breast milk, therefore, nursing should be discontin- ued during verapamil use.

Adverse Reactions: Constipation (7.9%), dizziness (3.2%), nausea (2.7%), headache (2.6%), headache (2.4%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dys- phoria (1.4%), bradycardia (1.4%), LV 3 (0.16%)). AV block 1, 2°, 3° (1%, 2%, and 3%). 0.8%, rash (1.2%), flushing (0.6%), elevated liver enzymes, reversible non-obstructive pan- creatic. The following are not related to the use of verapamil: patients, occurred under conditions where a causal relationship is uncertain: angina pectoris, arrhythmia, back pain, chest pain, claudication, myocardial infarction, palpitations, purpura, ischemic syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, croup, edema, flushing, glossitis, hiccups, rash, visual disturbances, vomiting, weight loss, skin rashes, flushing, urinary retention, increased urination, edema, interstitial nephritis, polyuria, rhinitis, swelling, sweating, thirst, vision, tremors, vasculitis, vertigo, vision, weight loss.

Address medical inquiries to: G.D. Searle & Co.

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For the Management of Mild to Moderate Hypertension

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ONCE-DAILY Calan® SR (verapamil HCl)
SUSTAINED-RELEASE CAPLETS

Excellence Built On Basics

The recommended starting dosage for Calan SR is 180 mg once daily. Dose titration will be required in some patients to achieve blood pressure control. A lower starting dosage of 120 mg/day may be warranted in some patients (e.g., the elderly, patients of small stature). Dosages above 360 mg daily should be administered in divided doses. Calan SR should be administered with food. Constipation, which is easily managed in most patients, is the most commonly reported side effect of Calan SR. Verapamil should be administered cautiously to patients with impaired renal function.

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