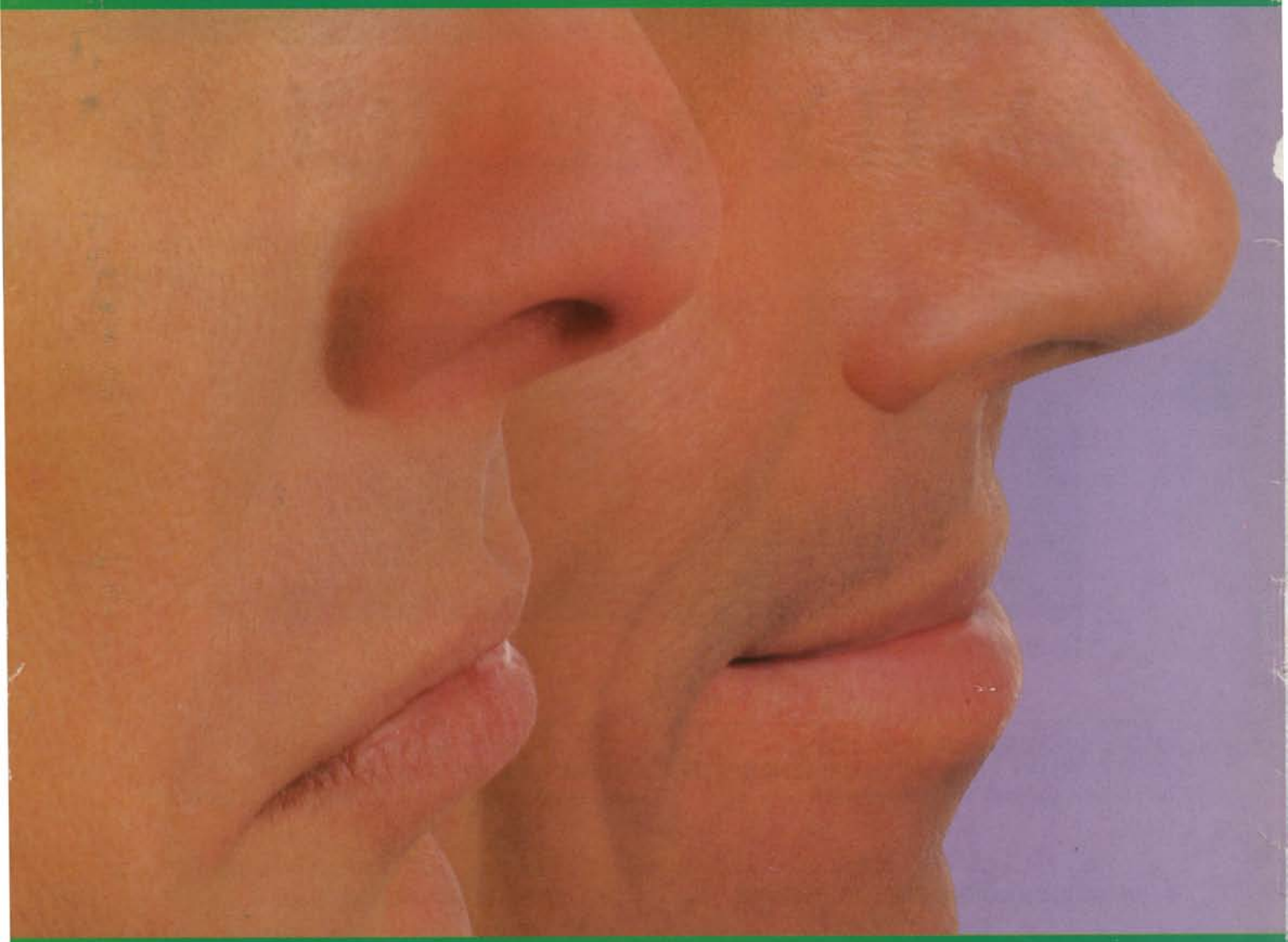
NOW versus Claritin®*!

FLONASE wins



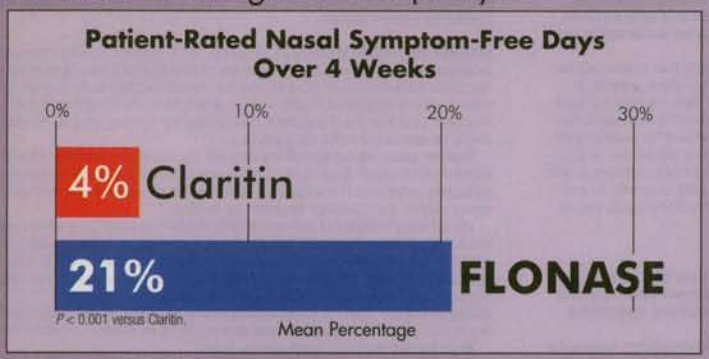
FLONASE is indicated for management of seasonal and perennial allergic rhinitis in patients 12 years and older. It is not indicated for nonallergic rhinitis.

* Claritin (loratadine) is a registered trademark of Schering Corp.

by a clear nose...

More nasal symptom-free days than Claritin†‡

In seasonal allergic rhinitis (SAR)...



Patients evaluated the following symptoms daily: daytime obstruction, rhinorrhea, sneezing, and itching.

† A multicenter, randomized, double-blind, double-dummy, parallel-group, 4-week study in 102 patients with SAR comparing FLONASE 200 µg QD and loratadine 10 mg QD.

‡ In a second multicenter, randomized, double-blind, double-dummy, parallel-group, 4-week study in 240 adolescent patients with SAR comparing FLONASE 200 µg QD and loratadine 10 mg QD, FLONASE demonstrated a significantly higher percentage of symptom-free days (20.5%) than loratadine (8.9%). $P<0.001$.

At a cost per day 30% less than Claritin§

	Adult Daily Dosage	AWP§	Cost Per Day
Claritin tablets	1 tablet QD	(100s) $193.54	**1.94**
FLONASE 120 actuations	one to two sprays/ nostril QD	$40.63	**.68-1.35**

§ Average wholesale price (AWP) based on *Redbook*®, November 1995. Prices presented may not necessarily reflect the actual prices paid by health care facilities or consumers.

Claritin Tablets exhibit an antihistaminic effect beginning within 1-3 hours, reaching its maximum at 8-12 hours.

A decrease in nasal symptoms has been noted in some patients 12 hours after initial treatment with FLONASE Nasal Spray. Maximum benefit may not be reached for several days. Effectiveness depends on regular use.

Side effects occurring at >1% (causal relationship possible) included epistaxis and nasal burning (3% to 6%) and nasal irritation, headache, and pharyngitis (1% to 3%).

Focused Relief Once a Day...

FLONASE®

(fluticasone propionate) QD AQ

NASAL SPRAY, 0.05%

ANTI-RHINITIC™ Benefits by Molecular Design

Please consult Brief Summary of Prescribing Information for FLONASE on adjacent page.

Flonase®
(fluticasone propionate)
Nasal Spray, 0.05% w/w

BRIEF SUMMARY

SHAKE GENTLY BEFORE USE.

For Intranasal Use Only.

The following is a brief summary only; see full prescribing information for complete product information.

CONTRAINDICATIONS: Flonase® Nasal Spray is contraindicated in patients with a hypersensitivity to any of its ingredients.

WARNINGS: The replacement of a systemic glucocorticoid with a topical glucocorticoid can be accompanied by signs of adrenal insufficiency, and in addition some patients may experience symptoms of withdrawal, e.g., joint and/or muscular pain, lassitude, and depression. Patients previously treated for prolonged periods with systemic glucocorticoids and transferred to topical glucocorticoids should be carefully monitored for acute adrenal insufficiency in response to stress. In those patients who have asthma or other clinical conditions requiring long-term systemic glucocorticoid treatment, too rapid a decrease in systemic glucocorticoids may cause a severe exacerbation of their symptoms.

The use of Flonase® Nasal Spray with alternate-day systemic prednisone could increase the likelihood of hypothalamic-pituitary-adrenal (HPA) suppression compared with a therapeutic dose of either one alone. Therefore, Flonase Nasal Spray should be used with caution in patients already receiving alternate-day prednisone treatment for any disease. In addition, the concomitant use of Flonase Nasal Spray with other inhaled glucocorticoids could increase the risk of signs or symptoms of hypercorticism and/or suppression of the HPA axis.

Patients who are on immunosuppressant drugs are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in patients on immunosuppressant doses of corticosteroids. In such patients who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information). If chickenpox develops, treatment with antiviral agents may be considered.

PRECAUTIONS:

General: Rarely, immediate hypersensitivity reactions or contact dermatitis may occur after the intranasal administration of fluticasone propionate. Rare instances of wheezing, nasal septum perforation, cataracts, glaucoma, and increased intraocular pressure have been reported following the intranasal application of glucocorticoids.

Use of excessive doses of glucocorticoids may lead to signs or symptoms of hypercorticism, suppression of HPA function, and/or suppression of growth in children or teenagers. Knemometry studies in asthmatic children on orally inhaled glucocorticoids showed inhibitory effects on short-term growth rate. The relationship between short-term changes in lower leg growth and long-term effects on growth is unclear at this time. Physicians should closely follow the growth of adolescents taking glucocorticoids, by any route, and weigh the benefits of glucocorticoid therapy against the possibility of growth suppression if an adolescent's growth appears slowed.

Although systemic effects have been minimal with recommended doses of Flonase® Nasal Spray, potential risk increases with larger doses. Therefore, larger than recommended doses of Flonase Nasal Spray should be avoided.

When used at larger doses, systemic glucocorticoid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, the dosage of Flonase Nasal Spray should be discontinued slowly consistent with accepted procedures for discontinuing oral glucocorticoid therapy.

In clinical studies with fluticasone propionate administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has occurred only rarely. When such an infection develops, it may require treatment with appropriate local therapy and discontinuation of treatment with Flonase Nasal Spray. Patients using Flonase Nasal Spray over several months or longer should be examined periodically for evidence of *Candida* infection or other signs of adverse effects on the nasal mucosa.

Flonase Nasal Spray should be used with caution, if at all, in patients with active or quiescent tuberculous infections; untreated fungal, bacterial, or systemic viral infections; or ocular herpes simplex.

Because of the inhibitory effect of glucocorticoids on wound healing, patients who have experienced recent nasal septal ulcers, nasal surgery, or nasal trauma should not use a nasal glucocorticoid until healing has occurred.

Information for Patients: Patients being treated with Flonase Nasal Spray should receive the following information and instructions. This information is intended to aid them in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Patients should be warned to avoid exposure to chickenpox or measles and, if exposed, to consult their physician without delay.

Patients should use Flonase Nasal Spray at regular intervals as directed since its effectiveness depends on its regular use. A decrease in nasal symptoms may occur as soon as 12 hours after starting therapy with Flonase Nasal Spray. Results in several clinical trials indicate statistically significant improvement within the first day or two of treatment; however, the full benefit of Flonase Nasal Spray may not be achieved until treatment has been administered for several days. The patient should not increase the prescribed dosage but should contact the physician if symptoms do not improve or if the condition worsens. For the proper use of the nasal spray and to attain maximum improvement, the patient should read and follow carefully the patient's instructions accompanying the product.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Fluticasone propionate demonstrated no tumorigenic potential in studies of oral doses up to 1.0 mg/kg (3 mg/m^2 as calculated on a surface area basis) for 78 weeks in the mouse or inhalation of up to 57 mcg/kg (336 mcg/m^2) for 104 weeks in the rat.

Fluticasone propionate did not induce gene mutation in prokaryotic or eukaryotic cells *in vitro*. No significant clastogenic effect was seen in cultured human peripheral lymphocytes *in vitro* or in the mouse micronucleus test when administered at high doses by the oral or subcutaneous routes. Furthermore, the compound did not delay erythroblast division in bone marrow.

No evidence of impairment of fertility was observed in reproductive studies conducted in rats dosed subcutaneously with doses up to 50 mcg/kg (295 mcg/m^2) in males and females. However, prostate weight was significantly reduced in rats.

Pregnancy: ***Teratogenic Effects: Pregnancy Category C:*** Subcutaneous studies in the mouse and rat at 45 and 100 mcg/kg, respectively (135 and 590 mcg/m^2, respectively, as calculated on a surface area basis), revealed fetal toxicity characteristic of potent glucocorticoid compounds, including embryonic growth retardation, omphalocele, cleft palate, and retarded cranial ossification.

In the rabbit, fetal weight reduction and cleft palate were observed following subcutaneous doses of 4 mcg/kg (48 mcg/m^2).

However, following oral administration of up to 300 mcg/kg (3.6 mg/m^2) of fluticasone propionate to the rabbit, there were no maternal effects nor increased incidence of external, visceral, or skeletal fetal defects. No fluticasone propionate was detected in the plasma in this study, consistent with the established low bioavailability following oral administration (see CLINICAL PHARMACOLOGY section of the full prescribing information).

Less than 0.008% of the dose crosses the placenta following oral administration to rats (100 mcg/kg, 590 mcg/m^2) or rabbits (300 mcg/kg, 3.6 mg/m^2).

There are no adequate and well-controlled studies in pregnant women. Fluticasone propionate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Experience with oral glucocorticoids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from glucocorticoids than humans. In addition, because there is a natural increase in glucocorticoid production during pregnancy, most women will require a lower exogenous glucocorticoid dose and many will not need glucocorticoid treatment during pregnancy.

Nursing Mothers: It is not known whether fluticasone propionate is excreted in human breast milk. Subcutaneous administration of tritiated drug to lactating rats (10 mcg/kg, 59 mcg/m^2) resulted in measurable radioactivity in both plasma and milk. Because other glucocorticoids are excreted in human milk, caution should be exercised when Flonase Nasal Spray is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of Flonase Nasal Spray in children below 12 years of age have not been established. Oral glucocorticoids have been shown to cause growth suppression in children and teenagers with extended use. If a child or teenager on any glucocorticoid appears to have growth suppression, the possibility that they are particularly sensitive to this effect of glucocorticoids should be considered (see PRECAUTIONS).

Geriatric Use: A limited number of patients above 60 years of age (n=132) have been treated with Flonase Nasal Spray in US and non-US clinical trials. While the number of patients is too small to permit separate analysis of efficacy and safety, the adverse reactions reported in this population were similar to those reported by younger patients.

ADVERSE REACTIONS: In controlled US studies, 2,427 patients received treatment with intranasal fluticasone propionate. In general, adverse reactions in clinical studies have been primarily associated with irritation of the nasal mucous membranes, and the adverse reactions were reported with approximately the same frequency by patients treated with the vehicle itself. The complaints did not usually interfere with treatment. Less than 2% of patients in clinical trials discontinued because of adverse events; this rate was similar for vehicle and active comparators.

Systemic glucocorticoid side effects were not reported during controlled clinical studies up to 6 months' duration with Flonase® Nasal Spray. If recommended doses are exceeded, however, or if individuals are particularly sensitive or if in conjunction with systemically administered glucocorticoids, symptoms of hypercorticism, e.g., Cushing's syndrome, could occur.

The following incidence of common adverse reactions is based upon seven controlled clinical trials in which 536 patients (57 girls and 108 boys aged 4 to 11 years, 137 female and 234 male adolescents and adults) were treated with Flonase Nasal Spray 200 mcg once daily over 2 to 4 weeks and two controlled clinical trials in which 246 patients (119 female and 127 male adolescents and adults) were treated with Flonase Nasal Spray 200 mcg once daily over 6 months.

Incidence Greater than 1% (Causal Relationship Possible): ***Respiratory:*** Epistaxis, nasal burning (incidence 3% to 6%); blood in nasal mucus, pharyngitis, nasal irritation (incidence 1% to 3%).

Neurological: Headache (incidence 1% to 3%).

Incidence Less than 1% (Causal Relationship Possible): ***Respiratory:*** Sneezing, runny nose, nasal dryness, sinusitis, nasal congestion, bronchitis, nasal ulcer, nasal septum excoriation.

Neurological: Dizziness.

Special Senses: Eye disorder, unpleasant taste.

Digestive: Nausea and vomiting, xerostomia.

Skin and Appendages: Urticaria.

Postmarketing Experience: In addition to the events from clinical trials, the following have been reported during postmarketing experience.

Hypersensitivity reactions, including skin rash, edema of the face and tongue, and rarely bronchospasm, have been reported.

OVERDOSAGE: There are no data available on the effects of acute or chronic overdosage with Flonase® Nasal Spray. Intranasal administration of 2 mg (10 times the recommended dose) of fluticasone propionate twice daily for 7 days to healthy human volunteers was well tolerated. Single oral doses up to 16 mg have been studied in human volunteers with no acute toxic effects reported. Repeat oral doses up to 80 mg daily for 10 days in volunteers and repeat oral doses up to 10 mg daily for 14 days in patients were well tolerated. Adverse reactions were of mild or moderate severity, and incidences were similar in active and placebo treatment groups. Acute overdosage with this dosage form is unlikely since one bottle of Flonase Nasal Spray contains approximately 8 mg of fluticasone propionate. Chronic overdosage may result in signs/symptoms of hypercorticism (see PRECAUTIONS).

GlaxoWellcome

Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

October 1995
RL-221
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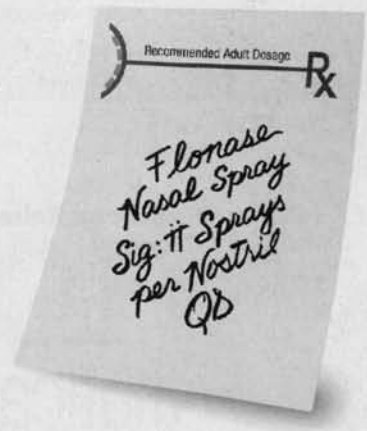
Manufactured in England



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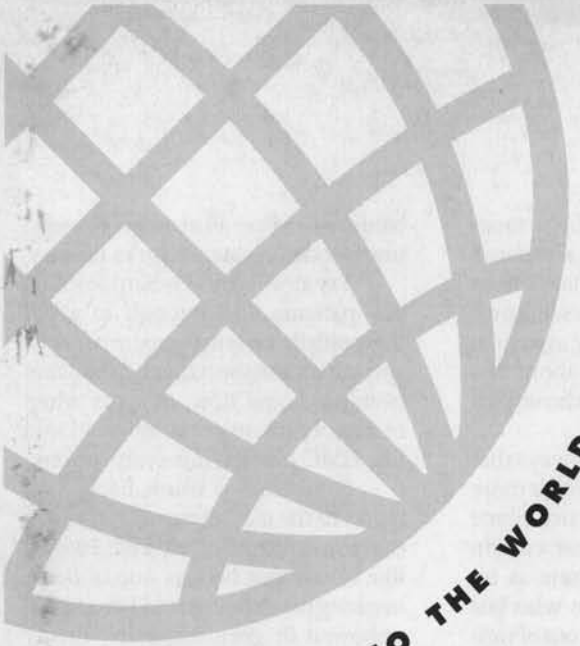

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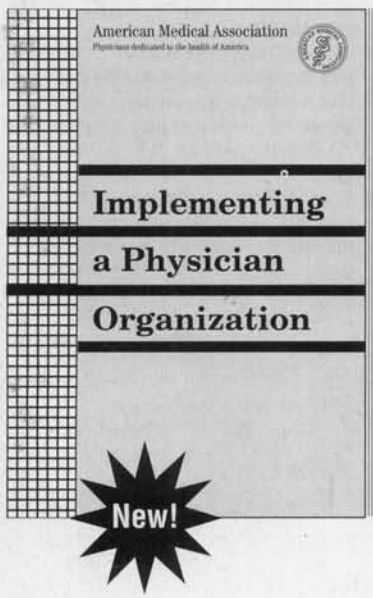

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The reminder system was very effective in this clinic population and improved the on-time injection rate to 96% when the 14-day grace period was included. Women receiving injections at this clinic were primarily young, single, white, and poor and had several prior pregnancies. It is not known how typical these women are when compared with medroxyprogesterone users in other locations in the United States. Because medroxyprogesterone was approved relatively recently, little has been published about its use in the United States. In a report of 199 primarily black, low–socioeconomic status adolescents, medroxyprogesterone was especially appealing to the teenagers who had been pregnant or had difficulty with oral contraceptive pills.[4] Although it is unknown whether a reminder system would be as effective in clinic settings with different patient demographics, its success with these women, who appear to be at high risk for contraceptive failure, is very encouraging. The study results also suggest that black and married women may be particularly at risk of receiving their injections late.

The reminder system used was a simple manual mail one that could be easily adapted to other clinic settings. Although telephone reminder systems have been successful in other settings,[2] telephone reminders were not considered for this study because of previously described difficulties in reaching clinic patients by telephone.[5] Although the mail reminder system was designed to require minimal nursing staff time, the time needed to determine the date of the patients' last Papanicolaou test was apparently time-consuming and frequently omitted. Unfortunately, many women inadvertently were quite late for their Papanicolaou testing. A computerized reminder system could potentially avoid this problem but would be more complex and expensive to initiate than a manual one.

In conclusion, clinics that offer medroxyprogesterone injections should consider providing a mail reminder system for their patients. However, clinics adopting such a system will need to ensure that other important preventive health services continue to be provided.

Accepted for publication October 6, 1995.

Correspondence to Department of Family and Community Medicine, St Paul Ramsey Medical Center, 640 Jackson St, St Paul, MN 55101 (Dr Madlon-Kay).

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As a family physician, who has been practicing acupuncture for 12 years, I am continually impressed by the depth that acupuncture has added to my practice. Acupuncture has given me another filter through which to sift the information that patients provide regarding their distress. Combining the Oriental and Western perspectives has enhanced my diagnostic ability as well as broadened the therapeutic options that I can offer my patients. As a result of integrating acupuncture into my practice, I believe that it has made me a better family practitioner.

Dr Peterson's article on acupuncture is a sign of the times. What was once considered a fringe medical technique is now slowly becoming established as an accepted medical modality. In fact, acupuncture has been endorsed as an accepted part of medical practice by the American Osteopathic Association, Chicago, Ill, since 1988, although the American Medical Association, Chicago, Ill, continues to regard acupuncture as an experimental medical modality. Presently, there are 3000 to 4000 physicians practicing acupuncture in the United States. Physicians who practice acupuncture are represented nationally by the American Academy of Medical Acupuncture, Santa Monica, Calif.

Acupuncture's clinical efficacy has been demonstrated in hundreds of thousands of patients in a multitude of cultures over at least 2500 years. Studies completed and now under way in the United States are confirming these millennia of clinical observations in Western terms. Acupuncture's mechanism of action remains obscure to us. Clearly, effects of acupuncture on neurotransmitter systems have been demonstrated, but much more work needs to be done. It is possible that the evolving fields of bioelectric medicine and quantum biology may have much more to offer us as to how acupuncture works. If this, indeed, becomes the case, then acupuncture and Western medicine may be the yin and yang of the medical system that is yet to come.

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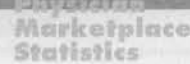

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Brief Summary of
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CARDIZEM® CD
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Capsules

CONTRAINDICATIONS
CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission.

WARNINGS
1. **Cardiac Conduction**. CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (13 of 3290 patients or 0.40%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure**. Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction 24% ± 6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Worsening of congestive heart failure has been reported in patients with preexisting impairment of ventricular function. Experience with the use of CARDIZEM (diltiazem hydrochloride) in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.
3. **Hypotension**. Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury**. Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 8 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in some cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS
General
CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters of renal and hepatic function should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.
Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interactions
Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with other agents known to affect cardiac contractility and/or conduction. (See WARNINGS.)
Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)
As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Especially in patients with renal and/or hepatic impairment, dosages of similarly metabolized drugs, particularly those of low therapeutic ratio, may require adjustment when starting or stopping concomitantly administered diltiazem to maintain optimum therapeutic blood levels.
Beta-blockers. Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities.
Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. In vitro, propranolol appears to be displaced from its binding sites by diltiazem. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)
Cimetidine. A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1200 mg per day and a single dose of diltiazem 60 mg. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.
Digitalis. Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)
Anesthetics. The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.
Cyclosporine. A pharmacokinetic interaction between diltiazem and cyclosporine has been observed during studies involving renal and cardiac transplant patients. In renal and cardiac transplant recipients, a reduction of cyclosporine dose ranging from 15% to 48% was necessary to maintain cyclosporine trough concentrations similar to those seen prior to the addition of diltiazem. If these agents are to be administered concurrently, cyclosporine concentrations should be monitored, especially when diltiazem therapy is initiated, adjusted, or discontinued.
The effect of cyclosporine on diltiazem plasma concentrations has not been evaluated.
Carbamazepine. Concomitant administration of diltiazem with carbamazepine has been reported to result in elevated serum levels of carbamazepine (40% to 72% increase), resulting in toxicity in some cases. Patients receiving these drugs concurrently should be monitored for a potential drug interaction.

Carcinogenesis, Mutagenesis, Impairment of Fertility
A 24-month study in rats at oral dosage levels of up to 100 mg/kg/day and a 21-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 dosages 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 perinatal/postnatal studies, there was an increased incidence of stillbirths at doses of 20 times the human dose or greater.
There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

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

Pediatric Use
Safety and effectiveness in pediatric patients 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 CARDIZEM CD up to 360 mg with rates in placebo patients shown for comparison.

CARDIZEM CD Capsule Placebo-Controlled Angina and Hypertension Trials Combined

Adverse Reactions	Cardizem CD (n=607)	Placebo (n=301)
Headache	5.4%	5.0%
Dizziness	3.0%	3.0%
Bradycardia	3.3%	1.3%
AV Block First Degree	3.3%	0.0%
Edema	2.6%	1.3%
ECG Abnormality	1.6%	2.3%
Asthenia	1.8%	1.7%

In clinical trials of CARDIZEM CD capsules, CARDIZEM tablets, and CARDIZEM SR capsules involving over 3200 patients, the most common events (ie, greater than 1%) were edema (4.6%), headache (4.6%), dizziness (3.5%), asthenia (2.6%), first-degree AV block (2.4%), bradycardia (1.7%), flushing (1.4%), nausea (1.4%), and rash (1.2%).
In addition, the following events were reported infrequently (less than 1%) in angina or hypertension trials:
Cardiovascular: Angina, arrhythmia, AV block (second- or third-degree), bundle branch block, congestive heart failure, ECG abnormalities, hypotension, palpitations, syncope, tachycardia, ventricular extrasystoles
Nervous System: Abnormal dreams, amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor
Gastrointestinal: Anorexia, constipation, diarrhea, dry mouth, dysgeusia, dyspepsia, mild elevations of SGOT, SGPT, LDH, and alkaline phosphatase (see hepatic warnings), thirst, vomiting, weight increase
Dermatological: Petechiae, photosensitivity, pruritus, urticaria
Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye irritation, hyperglycemia, hyperuricemia, impotence, muscle cramps, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties
The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, erythema multiforme (including Stevens-Johnson syndrome, toxic epidermal necrolysis), exfoliative dermatitis, extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, increased bleeding time, leukopenia, purpura, retinopathy, and thrombocytopenia. In addition, events such as myocardial infarction have been observed which are not readily distinguishable from the natural history of the disease in these patients. A number of well-documented cases of generalized rash, characterized as leukocytoclastic vasculitis, have been reported. However, a definitive cause and effect relationship between these events and CARDIZEM therapy is yet to be established.

Prescribing Information as of April 1995

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*Cardizem CD is a benzothiazepine calcium channel blocker.

† In clinical trials with Cardizem CD.
‡ FDA does not, at this time, consider other diltiazems to be therapeutically equivalent because bioequivalence has not been demonstrated through appropriate studies.

Please see brief summary of prescribing information on adjacent page.

FOR HYPERTENSION OR ANGINA

ONCE-A-DAY
CARDIZEM® CD
(diltiazem HCl) 120-, 180-, 240-, 300-mg Capsules

No other diltiazem is therapeutically equivalent[4‡]

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