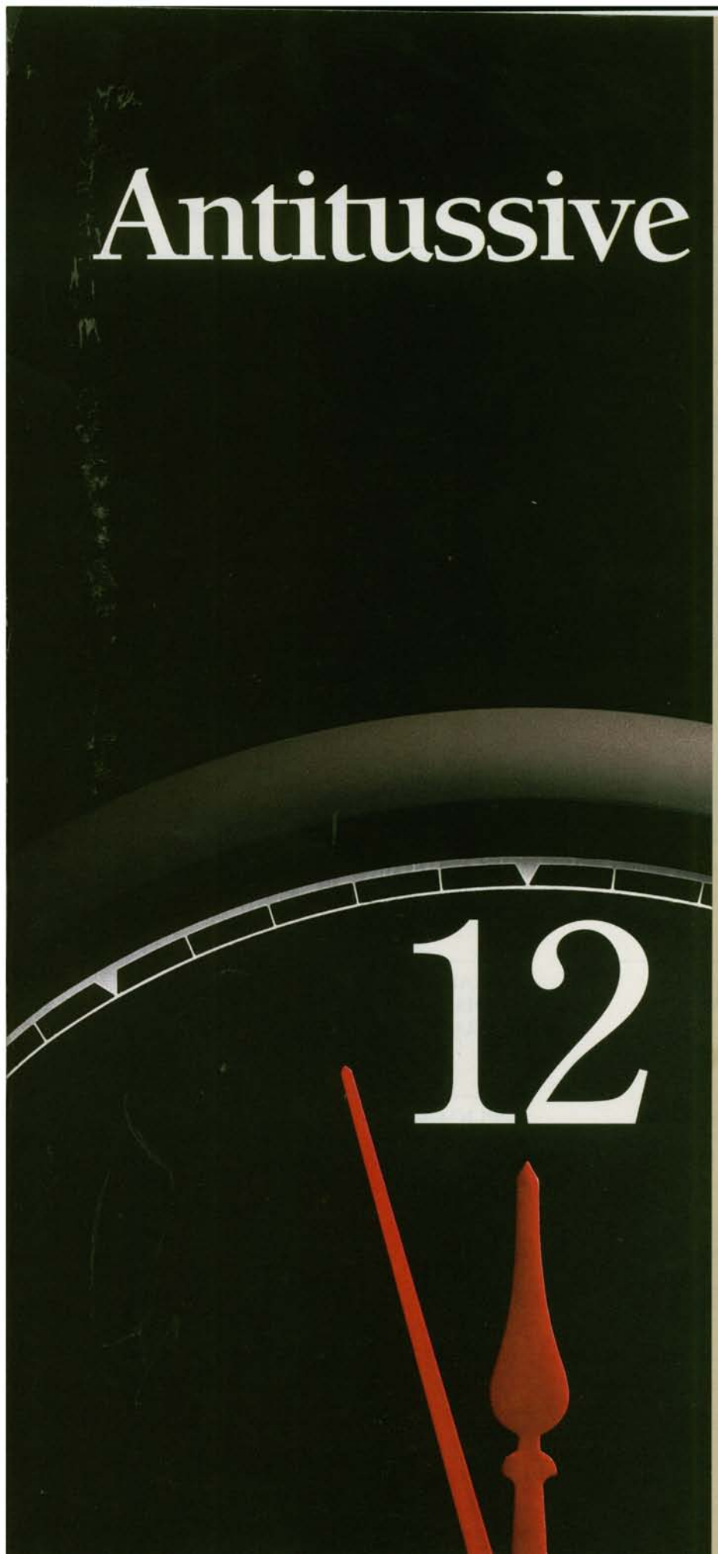
Antitussive 12 Hour Power.



- The only 12-hour liquid hydrocodone
- No middle-of-the-night or mid-day dosing
- Contains no iodinated glycerol
- One of the most economical prescription antitussives [1]
- The most frequently prescribed liquid hydrocodone [2]

Please see following page for Full Prescribing Information, including complete precautionary information.

TUSSIONEX is contraindicated in the presence of known allergy to hydrocodone or chlorpheniramine. The most common adverse reactions are sedation, drowsiness, and mental clouding, which may impair the mental and/or physical abilities required for potentially hazardous tasks, such as driving a car or operating machinery.

Tussionex® CIII

PENNKINETIC®

(hydrocodone polistirex (Warning: May be habit forming) */ chlorpheniramine polistirex)*

Extended-Release Suspension

Each teaspoonful (5 mL) provides the equivalent of 10 mg hydrocodone bitartrate and 8 mg chlorpheniramine maleate.

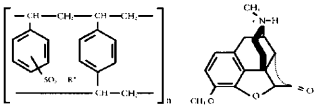
References from previous page: 1. Based on recommended adult maximum dose cited in the 1994 *Physician's Desk Reference* and 30% markup of the average wholesale price (AWP) cited in the November 1994 *Drug Topics Red Book*. 2. IMS Prescription Audit, November 1994.

TUSSIONEX® C II

Pennkinetic®
(hydrocodone polistirex
[Warning: May be habit forming]
and chlorpheniramine polistirex)
Extended-Release Suspension

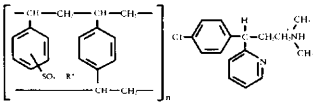
DESCRIPTION: Each teaspoonful (5 mL) of TUSSIONEX® Pennkinetic® Extended-Release Suspension contains hydrocodone polistirex equivalent to 10 mg of hydrocodone bitartrate (Warning: May be habit-forming) and chlorpheniramine polistirex equivalent to 8 mg of chlorpheniramine maleate. TUSSIONEX Pennkinetic Extended-Release Suspension provides up to 12-hour relief per dose. Hydrocodone is a centrally-acting narcotic antitussive. Chlorpheniramine is an antihistamine. TUSSIONEX Pennkinetic Extended-Release Suspension is for oral use only.

Hydrocodone Polistirex: sulfonated styrene-divinylbenzene copolymer complex with 4,5 α-epoxy-3-methoxy-17-ethylmorphinan-6-one.



Where R^+ = protonated hydrocodone

Chlorpheniramine Polistirex: sulfonated styrene-divinylbenzene copolymer complex with 2-[*p*-chloro-α-[2-(dimethyl-amino)ethyl]-benzyl]pyridine



Where R^+ = protonated chlorpheniramine

Other ingredients in TUSSIONEX Pennkinetic Extended-Release Suspension: Ascorbic acid, D&C Yellow No. 10, ethylcellulose, FD&C Yellow No. 6, flavor, high fructose corn syrup, methylparaben, polyethylene glycol 3350, polysorbate 80, pregelatinized starch, propylene glycol, propylparaben, purified water, sucrose, vegetable oil, xanthan gum.

CLINICAL PHARMACOLOGY: Hydrocodone is a semisynthetic narcotic antitussive and analgesic with multiple actions qualitatively similar to those of codeine. The precise mechanism of action of hydrocodone and other opiates is not known; however, hydrocodone is believed to act directly on the cough center. In excessive doses, hydrocodone, like other opium derivatives, will depress respiration. The effects of hydrocodone in therapeutic doses on the cardiovascular system are insignificant. Hydrocodone can produce miosis, euphoria, physical and psychological dependence.

Chlorpheniramine is an antihistamine drug (H_1 receptor antagonist) that also possesses anticholinergic and sedative activity. It prevents released histamine from dilating capillaries and causing edema of the respiratory mucosa.

Hydrocodone release from TUSSIONEX Pennkinetic Extended-Release Suspension is controlled by the Pennkinetic® System, an extended-release drug delivery system which combines an ion-exchange polymer matrix with a diffusion rate-limiting permeable coating. Chlorpheniramine release is prolonged by use of an ion-exchange polymer system. Following multiple dosing with TUSSIONEX Pennkinetic Extended-Release Suspension, hydrocodone mean (S.D.) peak plasma concentrations of 22.8 (5.9) ng/mL occurred at 3.4 hours. Chlorpheniramine mean (S.D.) peak plasma concentrations of 58.4 (14.7) ng/mL occurred at 6.3 hours following multiple dosing. Peak plasma levels obtained with an immediate-release syrup occurred at approximately 1.5 hours for hydrocodone and 2.8 hours for chlorpheniramine. The plasma half-lives of hydrocodone and chlorpheniramine have been reported to be approximately 4 and 16 hours, respectively.

INDICATIONS AND USAGE: TUSSIONEX Pennkinetic Extended-Release Suspension is indicated for relief of cough and upper respiratory symptoms associated with allergy or a cold.

CONTRAINDICATIONS: Known allergy or sensitivity to hydrocodone or chlorpheniramine.

WARNINGS:

Respiratory Depression: As with all narcotics, TUSSIONEX Pennkinetic Extended-Release Suspension produces dose-related respiratory depression by directly acting on brain stem respiratory centers. Hydrocodone affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing. Caution should be exercised when TUSSIONEX Pennkinetic Extended-Release Suspension is used postoperatively and in patients with pulmonary disease or whenever ventilatory function is depressed. If respiratory depression occurs, it may be antagonized by the use of naloxone hydrochloride and other supportive measures when indicated (see OVERDOSAGE).

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions: The administration of narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

Obstructive Bowel Disease: Chronic use of narcotics may result in obstructive bowel disease especially in patients with underlying intestinal motility disorder.

Pediatric Use: In young children, as well as adults, the respiratory center is sensitive to the depressant action of narcotic cough suppressants in a dose-dependent manner. Benefit to risk ratio should be carefully considered especially in children with respiratory embarrassment (e.g., croup). (See PRECAUTIONS.)

PRECAUTIONS: General: Caution is advised when prescribing this drug to patients with narrow-angle glaucoma, asthma or prostatic hypertrophy.

Special Risk Patients: As with any narcotic agent, TUSSIONEX Pennkinetic Extended-Release Suspension should be used with caution in elderly or debilitated patients and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind.

Information for Patients: As with all narcotics, TUSSIONEX Pennkinetic Extended-Release Suspension may produce marked drowsiness and impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery; patients should be cautioned accordingly. TUSSIONEX Pennkinetic Extended-Release Suspension must not be diluted with fluids or mixed with other drugs as this may alter the resin-binding and change the absorption rate, possibly increasing the toxicity. Keep out of the reach of children.

Cough Reflex: Hydrocodone suppresses the cough reflex; as with all narcotics, caution should be exercised when TUSSIONEX Pennkinetic Extended-Release Suspension is used postoperatively, and in patients with pulmonary disease.

Drug Interactions: Patients receiving narcotics, antihistamines, antipsychotics, antianxiety agents or other CNS depressants (including alcohol) concomitantly with TUSSIONEX Pennkinetic Extended-Release Suspension may exhibit an additive CNS depression. When combined therapy is contemplated, the dose of one or both agents should be reduced.

The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone.

The concurrent use of other anticholinergics with hydrocodone may produce paralytic ileus.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity, mutagenicity and reproductive studies have not been conducted with TUSSIONEX Pennkinetic Extended-Release Suspension.

Pregnancy

Teratogenic Effects — Pregnancy Category C: Hydrocodone has been shown to be teratogenic in hamsters when given in doses 700 times the human dose. There are no adequate and well-controlled studies in pregnant women. TUSSIONEX Pennkinetic Extended-Release Suspension should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose.

Labor and Delivery: As with all narcotics, administration of TUSSIONEX Pennkinetic Extended-Release Suspension to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

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

Pediatric Use: Safety and effectiveness of TUSSIONEX Pennkinetic Extended-Release Suspension in children under six have not been established.

ADVERSE REACTIONS: Central Nervous System: Sedation, drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, euphoria, dizziness, psychic dependence, mood changes.

Dermatologic System: Rash, pruritus.

Gastrointestinal System: Nausea and vomiting may occur; they are more frequent in ambulatory than in recumbent patients. Prolonged administration of TUSSIONEX Pennkinetic Extended-Release Suspension may produce constipation.

Genitourinary System: Ureteral spasm, spasm of vesicle sphincters and urinary retention have been reported with opiates.

Respiratory Depression: TUSSIONEX Pennkinetic Extended-Release Suspension may produce dose-related respiratory depression by acting directly on brain stem respiratory centers (see OVERDOSAGE).

Respiratory System: Dryness of the pharynx, occasional tightness of the chest.

DRUG ABUSE AND DEPENDENCE: TUSSIONEX Pennkinetic Extended-Release Suspension is a Schedule III narcotic. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of narcotics; therefore, TUSSIONEX Pennkinetic Extended-Release Suspension should be prescribed and administered with caution. However, psychic dependence is unlikely to develop when TUSSIONEX Pennkinetic Extended-Release Suspension is used for a short time for the treatment of cough. Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportions only after several weeks of continued oral narcotic use, although some mild degree of physical dependence may develop after a few days of narcotic therapy.

OVERDOSAGE: Signs and Symptoms: Serious overdosage with hydrocodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. Although miosis is characteristic of narcotic overdose, mydriasis may occur in terminal narcosis or severe hypoxia. In severe overdosage apnea, circulatory collapse, cardiac arrest and death may occur. The manifestations of chlorpheniramine overdosage may vary from central nervous system depression to stimulation.

Treatment: Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonist naloxone hydrochloride is a specific antidote for respiratory depression which may result from overdosage or unusual sensitivity to narcotics including hydrocodone. Therefore, an appropriate dose of naloxone hydrochloride should be administered, preferably by the intravenous route, simultaneously with efforts at respiratory resuscitation. Since the duration of action of hydrocodone in this formulation may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. For further information, see full prescribing information for naloxone hydrochloride. An antagonist should not be administered in the absence of clinically significant respiratory depression. Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated. Gastric emptying may be useful in removing unabsorbed drug.

DOSAGE AND ADMINISTRATION: Shake well before using. Adults: 1 teaspoonful (5 mL) every 12 hours; **do not exceed 2 teaspoonfuls in 24 hours.** Children 6-12: 1/2 teaspoonful every 12 hours; **do not exceed 1 teaspoonful in 24 hours.** Not recommended for children under 6 years of age (see PRECAUTIONS).

HOW SUPPLIED: TUSSIONEX Pennkinetic (hydrocodone polistirex and chlorpheniramine polistirex) Extended-Release Suspension is a gold-colored suspension available in bottles of one pint (473 mL) (NDC 0585-0548-67) and 900 mL (NDC 0585-0548-91).

Shake well. Dispense in a well-closed container. Store at 59°-86° F (15°-30° C).

Caution: Federal law prohibits dispensing without prescription.

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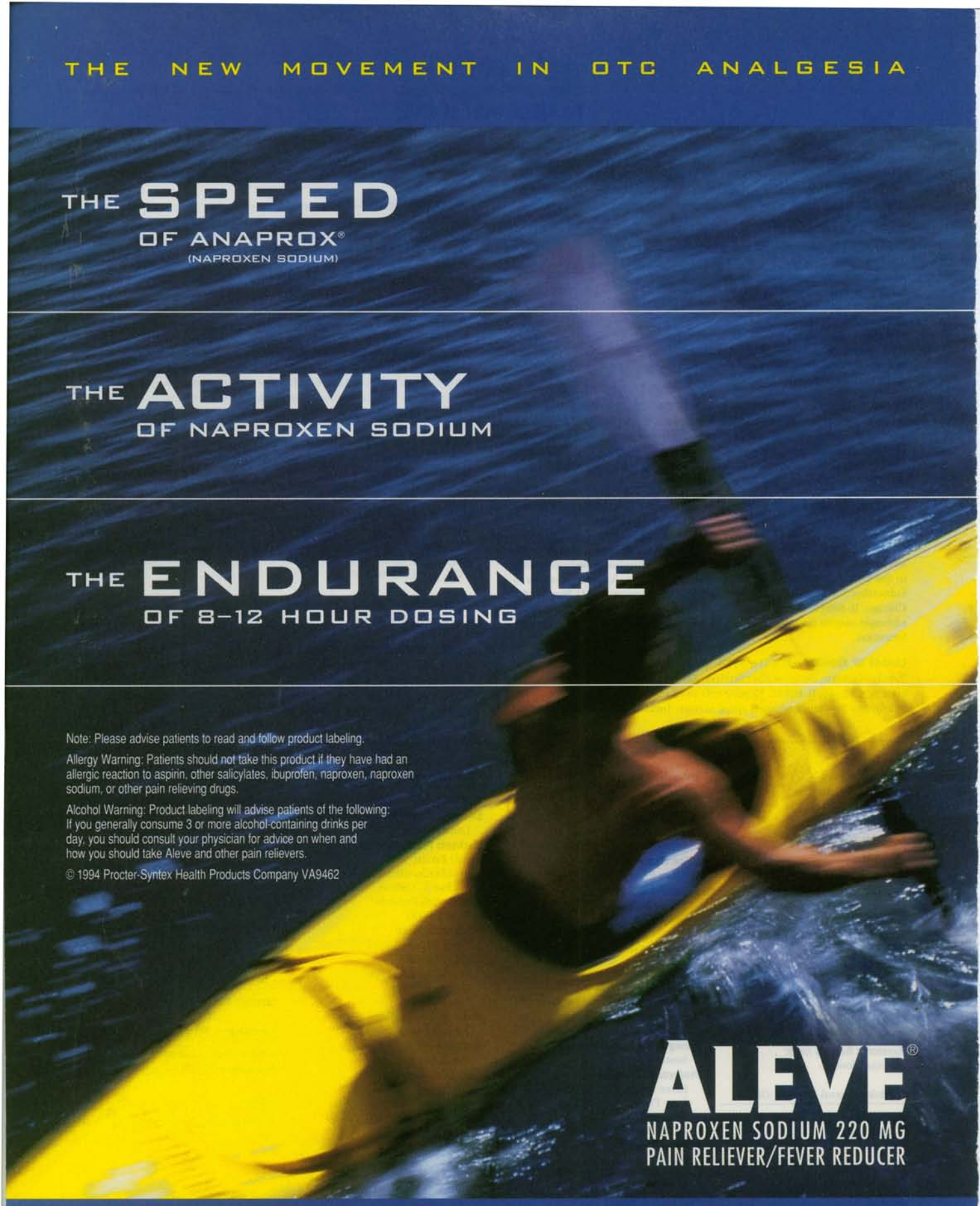

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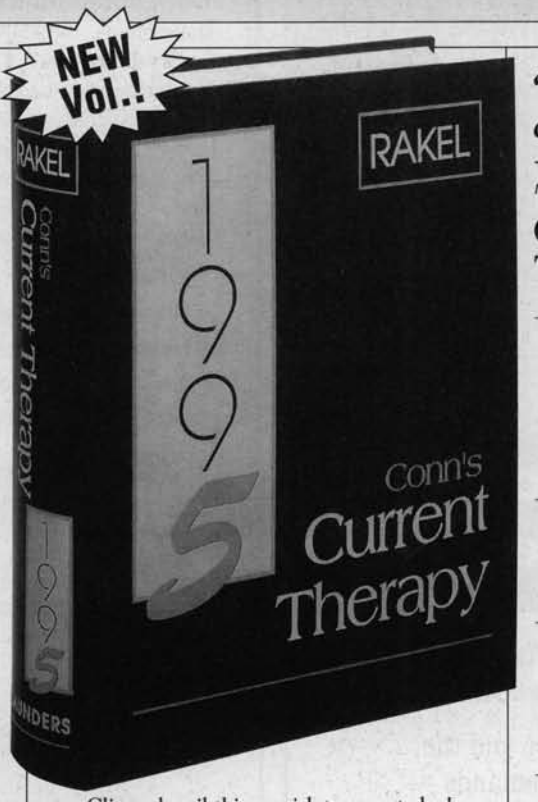

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Please consult Brief Summary of Prescribing Information on adjacent page.

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BRIEF SUMMARY

SHAKE GENTLY BEFORE USE.

For Intranasal Use Only.

The following is a brief summary only. Before prescribing, see complete prescribing information in Flonase™ Nasal Spray product labeling.

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.

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).

Allen & Hanburys
DIVISION OF GLAXO INC
Research Triangle Park, NC 27709

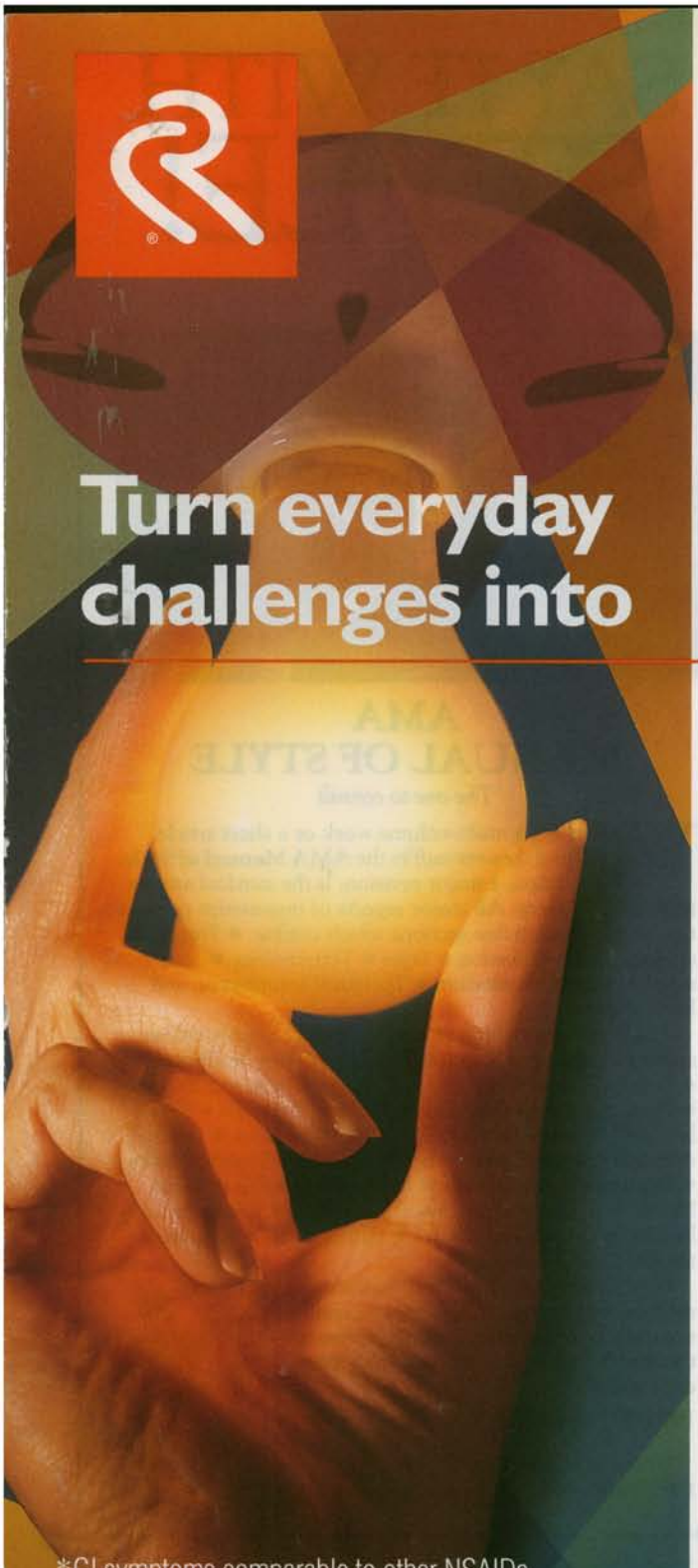
October 1994
RL-148
OM.BS.A

Recommended Adult Dosage Rx

Flonase Nasal Spray
Sig: II Sprays per Nostril QD

Allen & Hanburys
DIVISION OF GLAXO INC.
a world leader in respiratory care
Research Triangle Park, NC 27709

FLN141R0 Printed in USA January 1995



Turn everyday challenges into everyday *activities*

*GI symptoms comparable to other NSAIDs, including diarrhea, dyspepsia, and abdominal pain. In patients treated chronically with NSAID therapy, serious GI toxicity such as perforation, ulceration, and bleeding can occur.

As with other NSAIDs, rare renal and hepatic reactions have been reported. Please see precautions section of prescribing information.

Contraindicated in patients who are hypersensitive to aspirin or other NSAIDs.

Please see brief summary of prescribing information on adjacent page.

Effective relief with a low incidence of peptic ulcer*

RELAFEN®
nabumetone

AQ Comfort and QD Convenience...

Just One Nasal Steroid Has Both:

NEW FLONASE™

(fluticasone propionate)

- A first-line therapy for management of seasonal and perennial allergic rhinitis in patients 12 years and older – not indicated for nonallergic rhinitis.
- Relief of nasal symptoms may begin within 12 hours.
- Maximum benefit may take several days. Onset of action and degree of relief may vary in individual patients.

- 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%).

Please consult Brief Summary of Prescribing Information on adjacent page.

Focused Relief for Allergic Rhinitis...

NEW FLONASE™ NASAL SPRAY, 0.05%

(fluticasone propionate) QD AQ

The Aqueous/Once-a-Day ANTI-RHINITIC™

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. Before prescribing, see complete prescribing information in Flonase™ Nasal Spray product labeling.

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.

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).

Allen & Hanburys
DIVISION OF GLAXO INC.
Research Triangle Park, NC 27709

October 1994
RL-148
OM.BS.A

Recommended Adult Dosage Rx

Flonase Nasal Spray
Sig: 1 Sprays per Nostril QD

Allen & Hanburys
DIVISION OF GLAXO INC.
a world leader in respiratory care
Research Triangle Park, NC 27709

FLN141R0 Printed in USA January 1995

ONCE-A-DAY CARDIZEM® CD

(diltiazem HCl) 120-, 180-, 240-, 300-mg Capsules

FOR HYPERTENSION OR ANGINA

℞ Cardizem CD Start with one 180-mg capsule daily

Brief Summary of
Prescribing Information as of April 1993

CARDIZEM® CD
(diltiazem HCl)
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 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 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, 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 1993

Marion Merrell Dow Inc.
Kansas City, MO 64114

ccdb0493a

References: 1. Cardizem CD prescribing information. **2.** Data on file, Marion Merrell Dow Inc.

MARION MERRELL DOW INC.
U S A
KANSAS CITY, MO 64114

IN HYPERTENSION OR ANGINA

CARDIZEM® CD

(diltiazem HCl) 120-, 180-, 240-, 300-mg Capsules

FOR EFFECTIVE 24-HOUR CONTROL

ONCE A DAY

A unique hemodynamic and safety profile for hypertension or angina[1,2]

- A side-effect discontinuation rate comparable to placebo in both hypertension and angina trials[2]
- 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%)[1]

Please see brief summary of prescribing information on adjacent page.