Turn everyday challenges

* 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.*
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**BRIEF SUMMARY**

**INDICATIONS AND USAGE**

Ambien (zolpidem tartrate) is indicated for the short-term treatment of insomnia characterized by difficulty with falling or staying asleep or both, and when use is for a limited period of time, not to exceed 7 days. Ambien should not be prescribed for patients who require a sedative-hypnotic over a longer period of time. The use of sedatives-hypnotics for the treatment of insomnia should be limited to short periods (7 to 10 days) because there is little evidence of their efficacy after extended use, and the potential for habituation and psychological dependence may occur after several weeks of continuous use.

**CONTRAINDICATIONS**

No known.

**WARNINGS**

Sedation may occur following the use of Zolpidem Tartrate, and this effect may last longer in patients with hepatic impairment. Patients should be cautioned against engaging in hazardous activities requiring mental alertness until it is determined that Zolpidem Tartrate does not adversely affect them. The possibility of psychomotor impairment should be considered in patients with a history of head injury, a history of severe somnolence, or a history of drug dependence or alcoholism. In patients with a history of alcoholism, increased sensitivity to Zolpidem Tartrate may make them susceptible to development of significant tolerance or physical dependence to it.

**PRECAUTIONS**

General Use in the elderly and for debilitated persons: Impaired motor and/or cognitive performance after repeated or severe use may occur. Patients should be carefully observed for signs and symptoms of sedation which may impair performance. Patients should be observed for signs and symptoms of drug dependence or withdrawal if the drug is abruptly discontinued. Use in patients with concomitant illness: Clinical experience with Ambien is limited to patients with hepatic or renal disease. Caution is advised in using Ambien in patients with diseases or conditions which may predispose them to hepatic or renal impairment. Although preliminary studies did not reveal sedative depressive effects in normal volunteers following single oral doses of 10 to 20 mg, the use of Ambien should be approached with caution in patients with compromised respiratory function, since sedative-hypnotic drugs may impair respiratory drive. Post-marketing reports of respiratory arrest in individuals most of whom were elderly have been received. Data in end-stage renal failure patients have not been obtained. Therefore, the use of Zolpidem Tartrate in these patients must be approached with caution. Use in patients with history of drug abuse: Patients with a history of drug abuse may be at increased risk of dependence with Zolpidem Tartrate. Use in patients with history of alcoholism: Alcoholics are at increased risk of developing Zolpidem Tartrate withdrawal syndrome. Use in patients with impaired hepatic function: Since Zolpidem Tartrate is metabolized by the liver, Zolpidem Tartrate should be used with caution in patients with impaired hepatic function. Use in patients with impaired renal function: Since Zolpidem Tartrate is excreted primarily by the kidneys, Zolpidem Tartrate should be used with caution in patients with impaired renal function.

**ADVERSE REACTIONS**

Zolpidem is not associated with significant respiratory depression in normal volunteers following single oral doses up to 20 mg. However, in otherwise normal patients who have chronic respiratory impairment, Zolpidem Tartrate may cause depression of respiratory drive. Post-marketing reports of respiratory arrest in individuals most of whom were elderly have been received. Data in end-stage renal failure patients have not been obtained. Therefore, the use of Zolpidem Tartrate in these patients must be approached with caution. Use in patients with history of drug abuse: Patients with a history of drug abuse may be at increased risk of dependence with Zolpidem Tartrate. Use in patients with history of alcoholism: Alcoholics are at increased risk of developing Zolpidem Tartrate withdrawal syndrome. Use in patients with impaired hepatic function: Since Zolpidem Tartrate is metabolized by the liver, Zolpidem Tartrate should be used with caution in patients with impaired hepatic function. Use in patients with impaired renal function: Since Zolpidem Tartrate is excreted primarily by the kidneys, Zolpidem Tartrate should be used with caution in patients with impaired renal function.

**Incidence of Treatment-Emergent Adverse Experiences in Efficacy Trials**

Study patients were primarily male, mean age 57 years, mean body weight 170 lb (77 kg), and mean daily dose of 10 mg of zolpidem. Incidence of treatment-emergent adverse experiences were assessed in randomized, double-blind, placebo-controlled clinical trials comparing Zolpidem Tartrate, tablet form, to placebo. The incidence of treatment-emergent adverse experiences in patients treated with Zolpidem Tartrate is presented in the following summary table. The incidence of adverse experiences was assessed using the following grading criteria: mild: does not interfere with daily activities; moderate: interferes with daily activities; severe: interferes with life or requiring hospitalization. The table includes incidence of adverse experiences: those that occurred at an incidence of 1% or greater in Zolpidem Tartrate-treated patients that were not observed in placebo-treated patients; and those that occurred at an incidence of 1% or greater in placebo-treated patients that were not observed in patients treated with Zolpidem Tartrate.

**Incidence of Treatment-Emergent Adverse Experiences in Long-term Placebo-Controlled Trials**

Study patients were primarily male, mean age 57 years, mean body weight 170 lb (77 kg), and mean daily dose of 10 mg of zolpidem. Incidence of treatment-emergent adverse experiences were assessed in randomized, double-blind, placebo-controlled clinical trials comparing Zolpidem Tartrate, tablet form, to placebo. The incidence of treatment-emergent adverse experiences in patients treated with Zolpidem Tartrate is presented in the following summary table. The incidence of adverse experiences was assessed using the following grading criteria: mild: does not interfere with daily activities; moderate: interferes with daily activities; severe: interferes with life or requiring hospitalization. The table includes incidence of adverse experiences: those that occurred at an incidence of 1% or greater in Zolpidem Tartrate-treated patients that were not observed in placebo-treated patients; and those that occurred at an incidence of 1% or greater in placebo-treated patients that were not observed in patients treated with Zolpidem Tartrate.

**DRUG ABUSE AND DEPENDENCE**

Controlled substances schedule IV: Abuse and dependence: Ambien contains Zolpidem, a CNS depressant that has been shown to produce abuse potential. The potential for abuse is increased in individuals with a history of alcoholism or drug abuse. Zolpidem should be given with caution to patients with a history of drug addiction or alcoholism. Because of the potential for abuse, it is important to reinforce that Zolpidem should be reserved for patients with documented insomniac complaints. Because of the potential for abuse, it is important to reinforce that Zolpidem should be reserved for patients with documented insomniac complaints.

**OVERDOSAGE**

Signs and symptoms: In patients given Zolpidem Tartrate at doses up to 20 mg, symptoms of CNS depression similar to those seen with other sedative-hypnotics have been reported. Clinical signs and symptoms include drowsiness, ataxia, hypnosis, respiratory depression, hypotension, hypertension, cardiovascular collapse, circulatory collapse, hypothermia, hypoventilation, cyanosis, subnormal body temperature, hypoglycemia, hypocalcemia, hypomagnesemia, hypophosphatemia, metabolic acidosis, hepatic coma, crushed bone, renal failure, renal tubular necrosis, eosinophilia, keratopathy, anaphylactic shock, pancreatitis, and necrotic changes in the adrenal glands. In patients pretreated with Zolpidem Tartrate, the risk of drug accumulation may increase the frequency or severity of these signs and symptoms. Following severe overdosage of Zolpidem Tartrate, respiratory depression, reduced level of consciousness, confusion, and ataxia have been reported in patients who experienced severe somnolence after use of the drug. There have been isolated reports of death in patients who ingested large quantities of Zolpidem Tartrate.

Caution: Federal law prohibits dispensing without prescription.

**References**

From a unique chemical class of non-benzodiazepine sleep agents

More sleep
Total sleep time is significantly increased compared with placebo. Patients fall asleep quickly; generally within 20 to 30 minutes.1,3

Better sleep
Awakenings were reduced, compared to placebo.

Through the night
No evidence of increased wakefulness during the last third of the night. Normal sleep stages are generally preserved1 (clinical significance unknown).

With no objective evidence of tolerance or rebound insomnia
In studies of up to 35 consecutive nights at recommended doses.1,2

Favorable safety and tolerability profile
Adverse events with dosages of ≤ 10 mg that were statistically significant vs placebo

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The ARCHIVES OF FAMILY MEDICINE (ISSN 1063-3987) is published monthly by the American Medical Association, 515 N State St, Chicago, IL 60610, and is an official publication of the Association. Second-class postage paid at Chicago and at additional mailing office. GST registration number R126-225-556. Canada Post International Publications Mail (Canadian Distribution) Sales Agreement No. 319600. Printed in the USA.

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Barbara L. Whitcomb, MD; Allan Prochazka, MD; Mary LoVerde, ANP; Richard L. Byyny, MD

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in other conditions, pseudoxanthoma elasticum is the most frequent systemic association.² Angioid streaks eventually appear in the majority of patients with pseudoxanthoma elasticum.

The pattern of yellow dots at the level of the retinal pigment epithelium has been called "peau d'orange" and is thought to be a precursor of angioid streaks.³ That such a dramatic fundus appearance causes little or no disturbance of the fluorescein angiogram is surprising.

Patients with angioid streaks are known to be susceptible to subretinal hemorrhage following even mild trauma. Our patient's condition suggests that this risk exists prior to the development of clinically evident angioid streaks.

This study was supported by grant EY01730 from the National Eye Institute, Rockville, Md (Dr Kalina), and by an award from Research to Prevent Blindness Inc, New York, NY (Dr Kalina).


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but with older people being the fastest growing segment of the population, we need to get to the well-accepted stage quickly or go broke paying for nursing homes.

Two pieces that appeared by coincidence the same day in our local newspaper explain why I think everyone should know about adult day centers. The first was an article about a tragedy in Pittsburgh, Pa, in which a man who felt he was alone in caring for his wife with Alzheimer’s disease shot her and then killed himself. The second was a short letter to the editor by a thankful husband whose wife was enrolled in an adult day center, and he described how much it meant to both of them. A day center can't transform total despair into contentment, but I can't help wondering whether the first man had access to one.

If you think I need a day center, please enroll me. If I object, look at it the same way you did when you left Jason and Dana at child day care the first time. Like them, I might make a fuss, but by the time you’re playing your first set of tennis, I’ll be too busy to notice you’re gone. At night I can have some pasta while watching a tape of an old golf tournament I’ve seen a hundred times before and still be in suspense at the outcome. What nursing home can match that?

Love,
Burton

PS. It’s easy to find the nearest adult day center. You can call our local senior citizen center, the local area agency on aging, the state Department of Aging Services, or the National Institute on Adult Daycare in Washington, DC, at (202) 479-1200.

Burton V. Reifler, MD, MPH
Bowman Gray School of Medicine
Winston-Salem, NC

Dr Reifler is director of Partners in Caregiving, a National Demonstration Program supported by The Robert Wood Johnson Foundation, New York, NY.

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Millions victimized by family members every year!

Another available publication titled Domestic Violence: A Directory of Protocols for Health Care Providers is an abstracted compilation of protocols and manuals to help providers overcome some of the barriers they commonly encounter in addressing the needs of victims of domestic violence prevention.

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- Relief of nasal symptoms may begin within 12 hours.
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- 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.
**Brief Summary**

For Intrasal Nasal Use Only.

**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 an adrenal insufficiency and, in addition, some patients may experience symptoms of withdrawal, e.g., joint and muscular pain, insomnia, and depression. Patients previously treated for prolonged periods with systemic glucocorticoids and transferred to topical glucocorticoids should be carefully monitored for clinical symptoms and signs of adrenal insufficiency. This is particularly important in 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 therapy for treatment of another disease. In addition, the concurrent 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.

**PRECAUTIONS:**

**General:** Rarely, immediate hypersensitivity reactions or contact dermatitis may occur after the intranasal administration of Flonase nasal spray. Rare instances of epistaxis or epistaxis-like events have been reported in patients treated with Flonase nasal spray, and increased intraocular pressure have been reported following the intranasal application of glucocorticoids. If prolonged courses of glucocorticoids may lead to signs or symptoms of hypercorticism, suppression of HPA function, and/or suppression of growth in children or teenagers. Kneemetry studies in asthmatic children on orally inhaled glucocorticoids showed inhibitory effects on short-term growth rates. The relationship between short-term and long-term effects on growth and pubertal development is unclear. This relationship is also not well understood in other species. Patients should be followed for the growth of adolescents taking glucocorticoids, by a main doctor, and weight benefits of glucocorticoid therapy against the possibility of growth suppression if an adolescent's growth appears stunted. Although systemic effects may be minimal with recommended doses of Flonase nasal spray, prolonged increases with higher doses. Therefore, longer 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 occur. If such an effect occurs, the dosage regimen should be decreased, with careful monitoring of the patient's response.

**Skin and Appendages:** Usually well tolerated. Overdosage: There are no data available on the effects of acute or chronic overdose with Flonase nasal spray. Recommended adult dosage of 2 mg (10 times the recommended adult dosage of 0.2 mg twice daily for 7 days to 7 days for healthy 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 14 days in volunteers and repeat oral doses up to 10 mg daily for 14 days in patients were well tolerated. Adverse reactions were 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 6 mg of fluticasone propionate. Chronic overdosage may result in signs/symptoms of hypercorticism (see PRECAUTIONS).

Allen & Hanbury's DIVISION OF GLAXO INC.
Research Triangle Park, NC 27709

Recommended Adult Dosage

Flonase Nasal Spray

Sig-n Sprays for Relief

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Recommended adult dosage

Flonase Nasal Spray

Sig-n Sprays for Relief

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Meet Dr. Maureen O'Regan.
She's an obstetrician in
northern Virginia, within sight of
the nation's Capitol.
She delivers babies in Virginia
where there's a limit on health
care liability awards.
Just across the Potomac River,
in Washington, D.C., there is no
limit, and malpractice insurance
costs at least $68,000 - more
than twice the cost in Virginia.
Dr. O'Regan would like to
deliver babies in Washington, but
the cost is too high and the risk is
too great.

She's not alone. One out of
eight obstetrician/gynecologists
nationally no longer delivers
babies. Other doctors all across
the country struggle with the
same dilemma.
Without liability caps, huge
amounts of money are spent on
defensive medicine. Physicians
must order more procedures and
tests than the patient really
needs. The trust between patient
and physician is threatened.
Congress can fix this. The
U.S. House of Representatives
has already passed a bill that
would set a $250,000 cap on
noneconomic damages. Now it's
up to the U.S. Senate.
Contact your U.S. Senators
now. Tell them to vote for Health
Care Liability Reform.
And let Dr. O'Regan deliver
babies wherever she's needed.

Write both U.S. Senators c/o U.S.
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* No increase over '94

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Newport Beach, California
June 22-25, 1995

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Physicians dedicated to the health of America
Give allergic noses relief for itchy eyes due to seasonal allergic conjunctivitis.

When seasonal allergies strike, it's not just the nose they ambush. The eyes are fair game, too. In fact, 8 out of 10 patients with allergic noses also suffer from itchy eyes due to seasonal allergic conjunctivitis. Stop the itch with ACULAR® Solution.

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So help rescue eyes from itching with ACULAR®, the #1 prescribed ophthalmic preparation for the #1 patient complaint of seasonal allergic conjunctivitis — ocular itch. Because annoying antigens prey on more than just the nose.

The most frequently reported adverse events have been transient stinging and burning on instillation (approximately 40%). Not for use while wearing soft contact lenses.

Please see adjacent page for prescribing information.
ACULAR®
(ketorolac tromethamine) 0.5% Sterile Ophthalmic Solution

INDICATIONS AND USAGE
ACULAR® ophthalmic solution is indicated for the relief of ocular itching due to seasonal allergic conjunctivitis.

CONTRAINDICATIONS
ACULAR® ophthalmic solution is contraindicated in patients while wearing soft contact lenses and in patients with previously demonstrated hypersensitivity to any of the ingredients in the formulation.

WARNINGS
There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetlic acid derivatives, and other nonsteroidal anti-inflammatory agents. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

With some nonsteroidal anti-inflammatory drugs, there exists the potential for increased bleeding time due to interference with thrombofile aggregation. There have been reports that ocularly applied nonsteroidal anti-inflammatory drugs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

PRECAUTIONS
General: It is recommended that ACULAR® ophthalmic solution be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: An 18-month study in mice at oral doses of ketorolac tromethamine equal to the parenteral MRHD (Maximum Recommended Human Dose) and a 24-month study in rats at oral doses 2.5 times the parenteral MRHD, showed no evidence of tumorogenicity. Ketorolac tromethamine was not mutagenic in Ames test, unscheduled DNA synthesis and repair, and in forward mutation assays. Ketorolac did not cause chromosome breakage in the in vivo mouse micronucleus assay. At 1590 μg/mL (approximately 1000 times the average human plasma levels) and at higher concentrations ketorolac tromethamine increased the incidence of chromosomal aberrations in Chinese hamster ovary cells. Impairment of fertility did not occur in male or female rats at oral doses of 9 mg/kg (53.1 mg/m²) and 16 mg/kg (94.4 mg/m²) respectively.

Pregnancy: Pregnancy Category C. Reproduction studies have been performed in rabbits, using daily oral doses at 3.6 mg/kg (42.35 mg/m²) and in rats at 10 mg/kg (59 mg/m²) during organogenesis. Results of these studies did not reveal evidence of teratogenicity to the fetus. Oral doses of ketorolac tromethamine at 1.5 mg/kg (8.6 mg/m²), which was half of the human oral exposure, administered after gestation day 17 caused dystocia and higher pup mortality in rats. There are no adequate and well-controlled studies in pregnant women. Ketorolac tromethamine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Caution should be exercised when ACULAR® is administered to a nursing woman.

Pediatric Use: Safety and efficacy in children have not been established.

ADVERSE REACTIONS
In patients with allergic conjunctivitis, the most frequent adverse events reported with the use of ACULAR® ophthalmic solution have been transient stinging and burning on instillation. These events were reported by approximately 40% of patients treated with ACULAR® ophthalmic solution. In all development studies conducted, other adverse events reported during treatment with ACULAR® include ocular irritation (3%), allergic reactions (3%), superficial ocular infections (0.5%) and superficial keratitis (1%).

ACULAR®, a registered trademark of Syntex (U.S.A.) Inc., is manufactured and distributed by Allergan, Inc. under license from its developer, Syntex (U.S.A.) Inc., Palo Alto, California, U.S.A.

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- 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.

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**SNEAK GENTLY BEFORE USE.**

**BRIEF SUMMARY**

**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 muscle pain, fatigue, and depression). Patients previously treated for prolonged periods with systemic glucocorticoids and transdermally to topical glucocorticoids should be carefully monitored for signs of adrenal insufficiency in response to stress. In some patients who have asthma or have had other clinical symptoms requiring long-term systemic glucocorticoid usage, 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 systemic side effects. Concurrent use of Flonase™ Nasal Spray 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 severe or even fatal course in patients on immunosuppressant dosages of corticosteroids. In such patients who have not had these diseases, particular caution should be taken to avoid exposure. However, the duration and frequency 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, varicella, or other viral infections in vitro with profound immunodeficiencies (e.g., may be indicated). (See the respective package inserts for complete 250 and 150 mg 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 worsening, nasal septum perforation, catarrhalis, cataracts, and increased intraocular pressure have been reported following the use in patients using glucocorticoids.

The use of excess doses of glucocorticoids may lead to signs or symptoms of hypercorticism, suppression of the HPA function, and/or suppression of growth in children and teenagers. Knoxemistry studies in asthmatic children on orally inhaled glucocorticoids showed inhibitory effects on short-term growth rate. The relationship between short-term changes in height and long-term effects on growth is uncertain 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 slows down.

While 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 rarely only 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 for evidence of infection or infection effects on the nasal mucosa. Flonase Nasal Spray should be used with caution, if at all, in patients with active or quiescent tuberculosis infection, untreated fungal, bacterial, or viral infections or other herpes simplex.

**Cardiovascular:** 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.**

**Cardiovascular:** Metabolism. Impairment of Fertility: In clinical studies, Fluticasone propionate demonstrated no tumorigenic potential in studies of oral doses up to 1.0 mg/kg (3 mg/m² as calculated on a surface area basis) for 78 weeks in the mouse or inhalation of up to 57 mg/kg (336 mg/m²) for 104 weeks in the rat. Fluticasone propionate did not induce genotoxic effects 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 induce erythroblast division in bone marrow.

There is no evidence of impairment of fertility was observed in reproductive studies conducted in rats dosed subchronically with doses up to 75 mg/kg (205 mg/m²) 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 mg/kg, respectively (10 and 25 mg/kg as calculated on a surface area basis), revealed fetal toxicity characteristics of potent glucocorticoid compounds, including embryonic growth retardation, amphimaphic, cleft palate, and retarded ossification. The drug did not cause weight reduction following subcutaneous doses of 4 mg/kg (48 mg/m²).

Fetal lung development and viability were not affected following oral administration of up to 300 mg/kg (43 mg/m²) of Fluticasone propionate to the rabbit, there were no maternal effects nor increased incidences 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 0.006% of the dose crosses the placenta following oral administration to rats (100 mg/kg, 550 mg/m²) or rabbits (300 mg/kg, 3.5 mg/m²).

**DOSAGE AND ADMINISTRATION**

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 oral glucocorticoids should be administered during pregnancy only if the mother's disease is life-threatening. Subcutaneous administration of triitated drug to lactating rats (10 mg/kg, 59 mg/m²) resulted in measurable radioactivity in both plasma and milk. Because other glucocorticoids are excreted in human milk, caution should be used when Flonase Nasal Spray is administered to a nursing woman.

**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 unusually sensitive, side effects similar to those observed with orally administered glucocorticosteroids, symptoms of hypercorticism, e.g., Cushing's syndrome, may 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 248 patients (96 male adolescents and adults) were treated with Flonase Nasal Spray 300 mcg once daily over 6 months.

**Incidence Greater than 1% (Causal Relationship Possible):** Respiratory: Epistaxis, nasal burning (incidence 3% to 6%);6.72% in the study of atopic dermatitis, pharyngitis, nasal irritation (incidence 1% to 3%).

**Neurologic/Headache: Headache (incidence 1% to 3%.)**

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

**Neurologic:** Dizziness, *Special Senses:* Eye disorders, 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 2 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 overdose 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).

**FLONASE™ NASAL SPRAY**

**Divil & Banhurys** 420-BF

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**DIVISION OF GLAXO INC**

**Research Triangle Park, NC 27709**

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25. Hahn DL. Strategies to promote basic clinical preventive services. Fam Med. 1994;26:77.
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CONTRAINdications: CARDIZEM is contraindicated in 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 60 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion determined by x-ray or autopsy.

WARNINGS:  
1. Cardiac Conduction: CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time.CARDIZEM should not be used in patients with a sick sinus syndrome. This effect may easily be manifested in abnormal slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (13 of 256 patients or 5%). Concomitant use of lidocaine with beta-blockers or digoxin may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole after a few mg of lidocaine.Use caution in patients with cardiac conduction disease associated with use of lidocaine.

2. Congestive Heart Failure: Although dilatation has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have shown no change in cardiac index nor consistent negative effects on contractility (study). An acute study of oral dilatation in patients with impaired ventricular function and first-degree AV block demonstrated an increase in d-diastolic pressure of 1.5 mm Hg in contrast to the increase of 2.0 mm Hg in patients with impaired ventricular function associated with second-degree AV block. This study was 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 returned to normal with continued therapy. Rare instances of a more serious elevation in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been reported. 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 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 subjects with renal and chronic ion and rat studies designed to produce toxicity, high doses of dilatation were associated with hepatic damage. In some subjects, hepatic enzymes, such as alkaline phosphatase, LDH, and SGOT, were elevated in some subjects with cardiac damage. The 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 therapy. Some subjects receiving CARDIZEM have had mild to moderate increases in hepatic transaminases and bilirubin; however, these changes were reversible with continued therapy. The effect of dilatation on liver function is unknown. In a study of 17 patients with cirrhosis, there was no significant change in the serum levels of LDH, SGOT, or SGPT. However, in a study of 12 patients with hepatic disease, there was a significant increase in the serum levels of LDH, SGOT, and SGPT. In addition, the increase in the serum levels of these enzymes was associated with an increase in the serum levels of bilirubin. The relationship to CARDIZEM is uncertain in some cases, but probable in some. (See PRECAUTIONS.)

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 conductivity and/or conduction. (See WARNINGS.) Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers with CARDIZEM. (See WARNINGS.) As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM under- goes hepatic metabolism and, therefore, concurrent use of agents which affect the metabolism of CARDIZEM or 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 dilatation 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.

Adverse Events: CARDIZEM (diltiazem hydrochloride) concomitantly in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. In vitro, propranolol binding sites to be displaced from its binding sites by dilatation. If combined therapy is initiated or withdrawn in combination with propranolol, an adjustment of the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak serum levels (50%) and area-under-the-curve (53%) at 1200 mg per day and a single dose of 250 mg, respectively, which produced smaller, nonstatistically significant 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 dilatation. Patients currently receiving dilatation therapy should be carefully monitored for a change in pharmacologic effect when initiating and discontinuing therapy with cimetidine. An adjustment in the dilatation dose may be required.

Digitoxin. 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 to avoid possible overdosage. (See WARNINGS.)

Anesthesiology: The depression of cardiac conductivity, contractility, and automatically 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 dilatation and cyclosporine has been observed during studies involving 15 transplant patients in renal and cardiac transplant recipients. A single administration of cyclosporine dose ranging from 15% to 45% was necessary to maintain cyclosporine trough concentrations similar to those seen prior to the addition of dilatation. If these agents are to be administered concurrently, cyclosporine concentrations should be monitored, especially when dilatation therapy is initiated, adjusted, or discontinued. The effect of cyclosporine on dilatation plasma concentrations has not been evaluated.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: A 24 month study in rats of oral daily doses of up to 100 mg/kg/day and a 21 month study in mice at oral dosage levels of up to 50 mg/kg/day showed no evidence of carcinogenicity. There was also no mutagenic response in bacterial or mammalian cell assays or in vitro in bacteria. No evidence of impaired fertility was observed in a study performed in mice 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 of dilatation.

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

Nursing Mothers: Dilatation 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, and 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 hypotension trials in patients receiving CARDIZEM up to 360 mg with rates in placebo patients for each adverse reaction.

Cardiovascular: Angina, arrhythmia, AV block (second- or third-degree), bundle branch block, congestive heart failure, ECG abnormalities, hypotension, palpitations, syncope, tachycardia, ventricular extrasystoles

Endocrine: Abnormalities of glucose, pain, depression, galactorrhea, hallucinations, insomnia, nervousness, paresthesia, personal mood change, somnolence, timidity, tremor

Gastrointestinal: Anorexia, constipation, diarrhea, dry mouth, dysgeusia, mild elevations of SGOT, SGPT, LDH, and alkaline phosphatase (see hepatic warnings), thirst, vomiting, weight increase

Dermatologic: Petechiae, photosensitivity, pruritus, urticaria

Other: Arthralgia, CVA, increased creatinine, dizziness, eye irritation, hypoglycemia, hypoproteinemia, impotence, muscle cramps, nasal congestion, nicturias, ectopic cardiac arrhythmia, oral leukoplakia, sensory difficulties

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, erythema multiforme, exfoliative dermatitis, extrapyramidal symptoms, gynecomastia, headache, increased bleeding time, leukopenia, purpura, retinopathy, and thrombocytopenia. In addition, events such as behavioral and mood disturbances, depression, dizziness, dyspnea, anxiety, chills, cough, dyspnea, fever, flushing, fever, chills, fever, edema, flushing (1%), nausea (1%), rash (1%), and rash (1%) have been reported.

In clinical trials of CARDIZEM capsules, CARDIZEM tablets, and CARDIZEM SR capsules involving over 3200 patients, the most common events are (greater than 1%) edema (4%), headache (4%), dizziness (3%), and diarrhea (2%).CARDIZEM capsules, tablets, and CAR...
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- 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%)\textsuperscript{4}

Please see brief summary of prescribing information on adjacent page.

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