

Online Tool Aims to Help Estimate Fracture Risk

BY SHERRY BOSCHERT
San Francisco Bureau

SAN FRANCISCO — New guidelines for preventing and treating osteoporosis and a new online tool to quantify the risk of future fracture should help providers target therapy to patients who are most likely to benefit from it.

"Quantitative fracture risk assessment has finally arrived," Dr. Marjorie M. Luckey said at the annual meeting of the Inter-

national Society for Clinical Densitometry.

In February 2008, the National Osteoporosis Foundation (NOF) updated the "Clinician's Guide to Prevention and Treatment of Osteoporosis," first published in 1999 and last revised in 2003 with only minor changes. The guidelines are available at www.nof.org along with a link to the beta version of the World Health Organization's fracture risk assessment tool, FRAX, at www.shef.ac.uk/FRAX.

Previous NOF guidelines applied only to

postmenopausal white women and based intervention recommendations entirely on a patient's T score, with some modification of the level of intervention based on clinical risk factors, said Dr. Luckey, medical director of the osteoporosis and metabolic bone disease center at St. Barnabas Ambulatory Care Center, Livingston, N.Y.

The new guidelines also include recommendations for men over age 50 years and postmenopausal women of races/ethnicities other than white and base the

thresholds for intervention largely on a patient's estimated 10-year fracture risk. The new document also updates the economic modeling that informs treatment recommendations.

"The 2008 NOF guidelines are a hybrid, rather than going entirely to fracture risk-based guidelines. There are some patients who will get treated based on their T score, and others who will get treated based on their fracture risk," said Dr. Luckey, also of Mount Sinai School of Medicine, New York. This should have the effect of shifting some treatment from younger patients who have modestly reduced bone density levels (T scores of -2.0 or better) to treat an older population, "which most of us think is an appropriate move to treat patients who are at high risk for fracture."



'Quantitative fracture risk assessment has finally arrived' but keep your clinical thinking cap on.

DR. LUCKEY

As in the previous guidelines, the benefits of a healthy lifestyle and adequate calcium and vitamin D levels are emphasized. Patients should be assessed clinically to determine if they are at risk for osteoporosis, and bone density testing should be done if appropriate. Treatment is recommended for patients with a previous hip or vertebral fracture, regardless of bone density, for patients with T scores of -2.5 or lower, and for osteopenic patients with T scores between -1.0 and -2.5 if they have secondary causes of osteoporosis that can affect fracture risk, such as being totally immobilized or on glucocorticoids.

A new recommendation in the 2008 guidelines is to consider treating osteopenic patients if their 10-year probability of hip fracture is 3% or greater or their 10-year risk of a major fracture is 20% or greater, using the FRAX model.

The guidelines have not changed recommendations for the 10 million U.S. residents with osteoporosis but only for those among the 34 million U.S. residents with osteopenia who have no history of fracture and are not immobilized or on steroids. "Their level of risk should be assessed using the 10-year fracture rate model," she said.

The quantitative risk assessment adds a tool for providers but clinical judgment to individualize treatment decisions is just as important. "These fracture risk estimates should be used to facilitate the discussion you have with a patient about whether or not to go on pharmacotherapy," Dr. Luckey emphasized.

The online FRAX tool allows users to choose models for different countries, with separate models in the United States for white, black, Hispanic, or Asian patients. The user answers questions about the patient's age, sex, weight, and height.

Questions about clinical risk factors include entries for current smoking, parental hip fracture, and patient history of fracture.

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*PGB: pregabalin

Other Adverse Reactions Observed During the Clinical Studies of LYRICA Following is a list of treatment-emergent adverse reactions reported by patients treated with LYRICA during all clinical trials. The listing does not include those events already listed in the previous tables or elsewhere in labeling, those events for which a drug cause was remote, those events which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life-threatening. Events are categorized by body system and listed in order of decreasing frequency according to the following definitions: *frequent* adverse reactions are those occurring on one or more occasions in at least 1/100 patients; *infrequent* adverse reactions are those occurring in 1/100 to 1/1000 patients; *rare* reactions are those occurring in fewer than 1/1000 patients. Events of major clinical importance are described in the *Warnings and Precautions* section. **Body as a Whole** — *Frequent*: Abdominal pain, Allergic reaction, Fever, *Infrequent*: Abscess, Cellulitis, Chills, Malaise, Neck rigidity, Overdose, Pelvic pain, Photosensitivity reaction, Suicide attempt, *Rare*: Anaphylactoid reaction, Ascites, Granuloma, Hangover effect, Intentional Injury, Retroperitoneal Fibrosis, Shock, Suicide. **Cardiovascular System** — *Infrequent*: Deep thrombophlebitis, Heart failure, Hypotension, Postural hypotension, Retinal vascular disorder, Syncope, *Rare*: ST Depressed, Ventricular Fibrillation. **Digestive System** — *Frequent*: Gastroenteritis, Increased appetite; *Infrequent*: Cholecystitis, Cholelithiasis, Colitis, Dysphagia, Esophagitis, Gastritis, Gastrointestinal hemorrhage, Melena, Mouth ulceration, Pancreatitis, Rectal hemorrhage, Tongue edema; *Rare*: Aphthous stomatitis, Esophageal Ulcer, Periodontal abscess. **Hemic and Lymphatic System** — *Frequent*: Echinomycosis; *Infrequent*: Anemia, Eosinophilia, Hypochromic anemia, Leukocytosis, Leukopenia, Lymphadenopathy, Thrombocytopenia; *Rare*: Myelofibrosis, Polycythemia, Prothrombin decreased, Purpura, Thrombocytulmia. **Metabolic and Nutritional Disorders** — *Rare*: Glucose Tolerance Decreased, Urate Crystalluria. **Musculoskeletal System** — *Frequent*: Arthralgia, Leg cramps, Myalgia, Myasthenia; *Infrequent*: Arthrosis; *Rare*: Chondrodystrophy, Generalized Spasm. **Nervous System** — *Frequent*: Anxiety, Depersonalization, Hypertonia, Hypesthesia, Libido decreased, Nystagmus, Paresthesia, Stupor, Twitching; *Infrequent*: Abnormal dreams, Agitation, Apathy, Aphasia, Circumoral paresthesia, Dysarthria, Hallucinations, Hostility, Hyperalgesia, Hyperesthesia, Hyperkinesia, Hypokinesia, Hypotonia, Libido increased, Myoclonus, Neuralgia, *Rare*: Addiction, Cerebellar syndrome, Cogwheel rigidity, Coma, Delirium, Delusions, Dysautonomia, Dyskinesia, Dystonia, Encephalopathy, Extraparalymidal syndrome, Guillain-Barré syndrome, Hypalgesia, Intracranial hypertension, Manic reaction, Paranoid reaction, Peripheral neuritis, Personality disorder, Psychotic depression, Schizophrenic reaction, Sleep disorder, Torticollis, Trismus. **Respiratory System** — *Rare*: Apnea, Atelectasis, Bronchiolitis, Hiccup, Laryngismus, Lung edema, Lung fibrosis, Yawn. **Skin and Appendages** — *Frequent*: Pruritus, *Infrequent*: Alopecia, Dry skin, Eczema, Hirsutism, Skin ulcer, Urticaria, Vesiculobullous rash; *Rare*: Angioedema, Exfoliative dermatitis, Lichenoid dermatitis, Melanosis, Nail Disorder, Petechial rash, Purpuric rash, Pustular rash, Skin atrophy, Skin necrosis, Skin nodule, Stevens-Johnson syndrome, Subcutaneous nodule. **Special senses** — *Frequent*: Conjunctivitis, Diplopia, Otitis media, Tinnitus; *Infrequent*: Abnormality of accommodation, Blepharitis, Dry eyes, Eye hemorrhage, Hyperacusis, Photophobia, Retinal edema, Taste loss, Taste perversion; *Rare*: Anisocoria, Blindness, Corneal ulcer, Exophthalmos, Extraocular palsy, Iritis, Keratitis, Keratoconjunctivitis, Miosis, Mydriasis, Night blindness, Ophthalmoplegia, Optic atrophy, Papilledema, Parosmia, Ptosis, Uveitis. **Urogenital System** — *Frequent*: Anorgasmia, Impotence, Urinary frequency, Urinary incontinence; *Infrequent*: Abnormal ejaculation, Albuminuria, Amenorrhea, Dysmenorrhea, Dysuria, Hematuria, Kidney calculus, Leukorrhea, Menorrhagia, Metrorrhagia, Nephritis, Oliguria, Urinary retention, Urine abnormality; *Rare*: Acute kidney failure, Balanitis, Bladder Neoplasm, Cervicitis, Dyspareunia, Epididymitis, Female lactation, Glomerulitis, Ovarian disorder, Pyelonephritis. **Comparison of Gender and Race** The overall adverse event profile of pregabalin was similar between women and men. There are insufficient data to support a statement regarding the distribution of adverse experience reports by race. **Post-marketing Experience** The following adverse reactions have been identified during postapproval use of LYRICA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. **Nervous System Disorders** — Headache. **Gastrointestinal Disorders** — Nausea, Diarrhea

USE IN SPECIFIC POPULATIONS

Pregnancy Pregnancy Category C. Increased incidences of fetal structural abnormalities and other manifestations of developmental toxicity, including lethality, growth retardation, and nervous and reproductive system functional impairment, were observed in the offspring of rats and rabbits given pregabalin during pregnancy, at doses that produced plasma pregabalin exposures (AUC) ≥ 5 times human exposure at the maximum recommended dose (MRD) of 600 mg/day. When pregnant rats were given pregabalin (500, 1250, or 2500 mg/kg) orally throughout the period of organogenesis, incidences of specific skull alterations attributed to abnormally advanced ossification (premature fusion of the jugal and nasal sutures) were increased at ≥ 1250 mg/kg, and incidences of skeletal variations and retarded ossification were increased at all doses. Fetal body weights were decreased at the highest dose. The low dose in this study was associated with a plasma exposure (AUC) approximately 17 times human exposure at the MRD of 600 mg/day. A no-effect dose for rat embryo-fetal developmental toxicity was not established. When pregnant rabbits were given LYRICA (250, 500, or 1250 mg/kg) orally throughout the period of organogenesis, decreased fetal body weight and increased incidences of skeletal malformations, visceral variations, and retarded ossification were observed at the highest dose. The no-effect dose for developmental toxicity in rabbits (500 mg/kg) was associated with a plasma exposure approximately 16 times human exposure at the MRD. In a study in which female rats were dosed with LYRICA (50, 100, 250, 1250, or 2500 mg/kg) throughout gestation and lactation, offspring growth was reduced at ≥ 100 mg/kg and offspring survival was decreased at ≥ 250 mg/kg. The effect on offspring survival was pronounced at doses ≥ 1250 mg/kg, with 100% mortality in high-dose litters. When offspring were tested as adults, neurobehavioral abnormalities (decreased auditory startle responding) were observed at ≥ 250 mg/kg and reproductive impairment (decreased fertility and litter size) was seen at 1250 mg/kg. The no-effect dose for pre- and postnatal developmental toxicity in rats (50 mg/kg) produced a plasma exposure approximately 2 times human exposure at the MRD. There are no adequate and well-controlled studies in pregnant women. LYRICA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery** The effects of LYRICA on labor and delivery in pregnant women are unknown. In the prenatal-postnatal study in rats, pregabalin prolonged gestation and induced dystocia at exposures ≥ 50 times the mean human exposure (AUC₀₋₂₄) of 123 $\mu\text{g}\cdot\text{hr}/\text{mL}$ at the maximum recommended clinical dose of 600 mg/day. **Nursing Mothers** It is not known if pregabalin is excreted in human milk; it is, however, present in the milk of rats. Because many drugs are excreted in human milk, and because of the potential for tumorigenicity shown for pregabalin in animal studies, 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** The safety and efficacy of pregabalin in pediatric patients have not been established. In studies in which pregabalin (50 to 500 mg/kg) was orally administered to young rats from early in the postnatal period (Postnatal Day 7) through sexual maturity, neurobehavioral abnormalities (deficits in learning and memory, altered locomotor activity, decreased auditory startle responding and habituation) and reproductive impairment (delayed sexual maturation and decreased fertility in males and females) were observed at doses ≥ 50 mg/kg. The neurobehavioral changes of acoustic startle persisted

at ≥ 250 mg/kg and locomotor activity and water maze performance at ≥ 500 mg/kg in animals tested after cessation of dosing and, thus, were considered to represent long-term effects. The low effect dose for developmental neurotoxicity and reproductive impairment in juvenile rats (50 mg/kg) was associated with a plasma pregabalin exposure (AUC) approximately equal to human exposure at the maximum recommended dose of 600 mg/day. A no-effect dose was not established. **Geriatric Use** In controlled clinical studies of LYRICA in neuropathic pain associated with diabetic peripheral neuropathy, 246 patients were 65 to 74 years of age, and 73 patients were 75 years of age or older. In controlled clinical studies of LYRICA in neuropathic pain associated with postherpetic neuralgia, 282 patients were 65 to 74 years of age, and 379 patients were 75 years of age or older. In controlled clinical studies of LYRICA in epilepsy, there were only 10 patients 65 to 74 years of age, and 2 patients who were 75 years of age or older. No overall differences in safety and efficacy were observed between these patients and younger patients. In controlled clinical studies of LYRICA in fibromyalgia, 106 patients were 65 years of age or older. Although the adverse reaction profile was similar between the two age groups, the following neurological adverse reactions were more frequent in patients 65 years of age or older: dizziness, vision blurred, balance disorder, tremor, confusional state, coordination abnormal, and lethargy. LYRICA is known to be substantially excreted by the kidney, and the risk of toxic reactions to LYRICA may be greater in patients with impaired renal function. Because LYRICA is eliminated primarily by renal excretion, the dose should be adjusted for elderly patients with renal impairment [see *Dosage and Administration*].

DRUG ABUSE AND DEPENDENCE

Controlled Substance LYRICA is a Schedule V controlled substance. LYRICA is not known to be active at receptor sites associated with drugs of abuse. As with any CNS active drug, physicians should carefully evaluate patients for history of drug abuse and observe them for signs of LYRICA misuse or abuse (e.g., development of tolerance, dose escalation, drug-seeking behavior). **Abuse** In a study of recreational users (N=15) of sedative/hypnotic drugs, including alcohol, LYRICA (450mg, single dose) received subjective ratings of "good drug effect," "high" and "liking" to a degree that was similar to diazepam (30mg, single dose). In controlled clinical studies in over 5500 patients, 4% of LYRICA-treated patients and 1% of placebo-treated patients overall reported euphoria as an adverse reaction, though in some patient populations studied, this reporting rate was higher and ranged from 1 to 12%. **Dependence** In clinical studies, following abrupt or rapid discontinuation of LYRICA, some patients reported symptoms including insomnia, nausea, headache or diarrhea [see *Warnings and Precautions*], suggestive of physical dependence.

OVERDOSAGE

Signs, Symptoms and Laboratory Findings of Acute Overdosage in Humans There is limited experience with overdose of LYRICA. The highest reported accidental overdose of LYRICA during the clinical development program was 8000 mg, and there were no notable clinical consequences. In clinical studies, some patients took as much as 2400 mg/day. The types of adverse reactions experienced by patients exposed to higher doses (≥ 900 mg) were not clinically different from those of patients administered recommended doses of LYRICA. **Treatment or Management of Overdose** There is no specific antidote for overdose with LYRICA. If indicated, elimination of unabsorbed drug may be attempted by emesis or gastric lavage; usual precautions should be observed to maintain the airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of the patient. A Certified Poison Control Center should be contacted for up-to-date information on the management of overdose with LYRICA. Although hemodialysis has not been performed in the few known cases of overdose, it may be indicated by the patient's clinical state or in patients with significant renal impairment. Standard hemodialysis procedures result in significant clearance of pregabalin (approximately 50% in 4 hours).

PATIENT COUNSELING INFORMATION

Patient Package Insert Patients should be informed of the availability of a patient information leaflet, and they should be instructed to read the leaflet prior to taking LYRICA. **Angioedema** Patients should be advised that LYRICA may cause angioedema, with swelling of the face, mouth (lip, gum, tongue) and neck (larynx and pharynx) that can lead to life-threatening respiratory compromise. Patients should be instructed to discontinue LYRICA and immediately seek medical care if they experience these symptoms [see *Warnings and Precautions*]. **Hypersensitivity** Patients should be advised that LYRICA has been associated with hypersensitivity reactions such as wheezing, dyspnea, rash, hives, and blisters. Patients should be instructed to discontinue LYRICA and immediately seek medical care if they experience these symptoms [see *Warnings and Precautions*]. **Dizziness and Somnolence** Patients should be counseled that LYRICA may cause dizziness, somnolence, blurred vision and other CNS signs and symptoms. Accordingly, they should be advised not to drive, operate complex machinery, or engage in other hazardous activities until they have gained sufficient experience on LYRICA to gauge whether or not it affects their mental, visual, and/or motor performance adversely [see *Warnings and Precautions*]. **Weight Gain and Edema** Patients should be counseled that LYRICA may cause edema and weight gain. Patients should be advised that concomitant treatment with LYRICA and a thiazolidinedione antidiabetic agent may lead to an additive effect on edema and weight gain. For patients with preexisting cardiac conditions, this may increase the risk of heart failure [see *Warnings and Precautions*]. **Abrupt or Rapid Discontinuation** Patients should be advised to take LYRICA as prescribed. Abrupt or rapid discontinuation may result in insomnia, nausea, headache, or diarrhea [see *Warnings and Precautions*]. **Ophthalmological Effects** Patients should be counseled that LYRICA may cause visual disturbances. Patients should be informed that if changes in vision occur, they should notify their physician [see *Warnings and Precautions*]. **Creatine Kinase Elevations** Patients should be instructed to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever [see *Warnings and Precautions*]. **CNS Depressants** Patients who require concomitant treatment with central nervous system depressants such as opiates or benzodiazepines should be informed that they may experience additive CNS side effects, such as somnolence. **Alcohol** Patients should be told to avoid consuming alcohol while taking LYRICA, as LYRICA may potentiate the impairment of motor skills and sedating effects of alcohol. **Use in Pregnancy** Patients should be instructed to notify their physician if they become pregnant or intend to become pregnant during therapy, and to notify their physician if they are breast feeding or intend to breast feed during therapy [see *Use in Specific Populations*]. **Male Fertility** Men being treated with LYRICA who plan to father a child should be informed of the potential risk of male-mediated teratogenicity. In preclinical studies in rats, pregabalin was associated with an increased risk of male-mediated teratogenicity. The clinical significance of this finding is uncertain. **Dermatopathy** Diabetic patients should be instructed to pay particular attention to skin integrity while being treated with LYRICA. Some animals treated with pregabalin developed skin ulcerations, although no increased incidence of skin lesions associated with LYRICA was observed in clinical trials.



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A question about glucocorticoid use does not specify past or current use, but the model “is most accurately used if the patient has been on 3 months or more of 5 mg of prednisone equivalent per day currently or in the recent past,” Dr. Luckey said.

The only secondary cause of osteoporosis specifically mentioned is rheumatoid arthritis. Although another question generically asks if the patient has another secondary cause of osteoporosis, “it’s a dummy variable” in the model that does not contribute to the online calculation of fracture risk, she noted.

A question about “alcohol 3 more units per day” is a typo that should read, “alcohol 3 or more units per day,” she added. A unit of alcohol is a standard glass of beer, an ounce of hard liquor, or a 4-ounce glass of weak wine. A 6-ounce glass of wine with 13%-14% alcohol content provides 2 units of alcohol.

Bone density can be entered as a T score or Z score. The model assumes that a T score was calculated using a white female reference database, so if you’re not sure what reference database was used to get a T score for nonwhite women, enter a Z score, she advised. Male T scores are based on a male database, so enter a Z

score in the FRAX model, which will convert a Z score to a T score.

Then click on the “calculate” button to get the estimated 10-year risk for hip fracture and all major fractures. The tool should not be used for premenopausal women, men under 50 years old, or patients who have started pharmacotherapy for bone health. It will underestimate risk in some patients because it does not include all risk factors and all secondary causes of osteoporosis. Keep your clinical thinking cap on, she advised.

Dr. Luckey is associated with multiple companies that make osteoporosis medications. She is a consultant and speaker for

Eli Lilly & Co. and Merck & Co., and she is a consultant and received grants from Amgen Inc. Dr. Luckey is a speaker and received grant funds from Proctor & Gamble Corp. She also is a speaker for Sanofi Aventis and Novartis Corp. and received grants from Roche/GlaxoSmithKline. ■

Yoga Does Not Improve Bone Mineral Density

SAN FRANCISCO — Three years of yoga practice did not change bone mineral density in 31 postmenopausal women, compared with bone densities in 31 inactive women.

Proponents of yoga have wondered whether it might produce bone benefits similar to those seen with weight-bearing exercises. Previous data have shown skeletal tissue responds to site-specific stresses.

Yoga consists of movements and poses using body weight as a form of resistance, and contorts the joints with torque and strain. Results of the current cross-sectional study suggest yoga doesn’t provide enough of a stimulus to increase bone mineral densities to levels significantly above those in inactive women, Millie Sweesy-Barger and associates said in a poster presentation at the annual meeting of the International Society for Clinical Densitometry.

Women in the yoga group had a 3-year history of practicing yoga at least twice a week in sessions of 60 minutes or longer. Those in the inactive group reported less than 2 hours of physical activity a week over the past 3 years. Participants underwent dual-energy x-ray absorptiometry (DXA) scans of the lumbar spine, left and right femurs, nondominant distal radius, and whole body. The mean age of the women was 60 years in the inactive group and 58 years in the yoga group. The cohort included 59 whites and 3 Asian Americans.

No significant differences between groups were seen in bone mineral densities at any sites. Higher mean bone mineral density in the distal radius in the inactive group, compared with the yoga group, became statistically insignificant after controlling for the effects of age, height, body mass, body mass index (BMI), percent body fat, fat mass, lean body mass, and calcium intake, said Ms. Sweesy-Barger, a student in the department of kinesiology and physical therapy at California State University, Long Beach. The yoga group had significantly lower mean measurements of body mass, percent body fat, fat mass, and BMI, compared with the inactive group, she added.

There is substantial evidence showing significant physical and psychological benefits of exercise programs for older adults, 55% of whom in the United States either have osteoporosis or are at risk of developing the disease, Ms. Sweesy-Barger noted. “To the aging, nonathletic postmenopausal woman, the question becomes, which activities are most effective for mitigating the loss of bone?”

Understanding how bone adapts to various forms of physical activity will help inform public health strategies to prevent and manage osteoporosis, she said.

—Sherry Boschert

OMNARIS™ (ciclesonide)

Nasal Spray, 50 mcg

For intranasal use only

Rx only

BRIEF SUMMARY: Please see package insert for full prescribing information.

INDICATIONS AND USAGE

Seasonal Allergic Rhinitis

OMNARIS Nasal Spray is indicated for the treatment of nasal symptoms associated with seasonal allergic rhinitis in adults and children 6 years of age and older.

Perennial Allergic Rhinitis

OMNARIS Nasal Spray is indicated for the treatment of nasal symptoms associated with perennial allergic rhinitis in adults and adolescents 12 years of age and older.

CONTRAINDICATIONS

OMNARIS Nasal Spray is contraindicated in patients with a hypersensitivity to any of its ingredients.

WARNINGS

The replacement of a systemic corticosteroid with a topical corticosteroid can be accompanied by signs of adrenal insufficiency. In addition, some patients may experience symptoms of corticosteroid withdrawal, e.g., joint and/or muscular pain, lassitude, and depression. Patients previously treated for prolonged periods with systemic corticosteroids and transferred to topical corticosteroids 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 corticosteroid treatment, rapid decreases in systemic corticosteroid dosages may cause a severe exacerbation of their symptoms.

Patients who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in children or adults using corticosteroids. In children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect 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

Intranasal corticosteroids may cause a reduction in growth velocity when administered to pediatric patients (see PRECAUTIONS: Pediatric Use). Rarely, immediate hypersensitivity reactions or contact dermatitis may occur after the administration of intranasal corticosteroids. Patients with a known hypersensitivity reaction to other corticosteroid preparations should use caution when using ciclesonide nasal spray since cross reactivity to other corticosteroids including ciclesonide may also occur.

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal septal ulcers, nasal surgery, or nasal trauma should not use a nasal corticosteroid until healing has occurred. In clinical studies with OMNARIS Nasal Spray, the development of localized infections of the nose and pharynx with *Candida albicans* has rarely occurred. When such an infection develops, it may require treatment with appropriate local therapy and discontinuation of OMNARIS Nasal Spray. Therefore, patients using OMNARIS 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. Intranasal corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract; or in patients with untreated local or systemic fungal or bacterial infections; systemic viral or parasitic infections; or ocular herpes simplex.

If recommended doses of intranasal corticosteroids are exceeded or if individuals are particularly sensitive or predisposed by virtue of recent systemic steroid therapy, symptoms of hypercorticism may occur, including very rare cases of menstrual irregularities, acneiform lesions, and cushingoid features. If such changes occur, topical corticosteroids should be discontinued slowly, consistent with accepted procedures for discontinuing oral steroid therapy.

The risk of glaucoma was evaluated by assessments of intraocular pressure in 3 studies including 943 patients. Of these, 390 adolescents or adults were treated for up to 52 weeks and 186 children ages 2 to 11 received treatment with OMNARIS Nasal Spray 200 mcg daily for up to 12 weeks. In these trials, no significant differences in intraocular pressure changes were observed between OMNARIS Nasal Spray 200 mcg and placebo-treated patients. Additionally, no significant differences between OMNARIS Nasal Spray 200 mcg and placebo-treated patients were noted during the 52-week study of adults and adolescent patients in whom thorough ophthalmologic assessments were performed including evaluation of cataract formation using slit lamp examinations. Rare instances of wheezing, nasal septum perforation, cataracts, glaucoma, and increased intraocular pressure have been reported following the intranasal application of corticosteroids. Close follow-up is warranted in patients with a change in vision and with a history of glaucoma and/or cataracts.

Information for Patients

Patients being treated with OMNARIS 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 who are on immunosuppressive doses of corticosteroids should be warned to avoid exposure to chickenpox or measles, and if exposed, to obtain medical advice. Patients should use OMNARIS Nasal Spray at regular intervals since its effectiveness depends on its regular use (see DOSAGE AND ADMINISTRATION).

In clinical trials, the onset of effect was seen within 24 to 48 hours with further symptomatic improvement observed over 1 to 2 weeks in seasonal allergic rhinitis and 5 weeks in perennial allergic rhinitis. Initial assessment of response should be made during this timeframe and periodically until the patients symptoms are stabilized.

The patient should take the medication as directed and should not exceed the prescribed dosage. The patient should contact the physician if symptoms do not improve by a reasonable time or if the condition worsens. For the proper use of this unit and to attain maximum improvement, the patients should read and follow the accompanying patient instructions carefully. Spraying OMNARIS Nasal Spray directly into the eyes or onto the nasal septum should be avoided. It is important that the bottle is gently shaken prior to use to ensure that a consistent amount is dispensed per actuation. The bottle should be discarded after 120 actuations following initial priming or after 4 months after the bottle is removed from the foil pouch, whichever occurs first.

Drug Interactions

Based on *in vitro* studies in human liver microsomes, des-ciclesonide appears to have no inhibitory or induction potential on the metabolism of other drugs metabolized by CYP 450 enzymes. The inhibitory potential of ciclesonide on CYP450 isoenzymes has not been studied. *In vitro* studies demonstrated that the plasma protein binding of des-ciclesonide was not affected by warfarin or salicylic acid, indicating no potential for protein binding-based drug interactions.

In a drug interaction study, co-administration of orally inhaled ciclesonide and oral erythromycin, an inhibitor of cytochrome P450 3A4, had no effect on the pharmacokinetics of either des-ciclesonide or erythromycin. In another drug interaction study, co-administration of orally inhaled ciclesonide and oral ketoconazole, a potent inhibitor of cytochrome P450 3A4, increased the exposure (AUC) of des-ciclesonide by approximately 3.6-fold at steady state, while levels of ciclesonide remained unchanged. Therefore, ketoconazole should be administered with caution with intranasal ciclesonide.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Ciclesonide demonstrated no carcinogenic potential in a study of oral doses up to 900 mcg/kg (approximately 20 to 10 times the maximum human daily intranasal dose in adults and children, respectively, based on mcg/m²) in mice for 104 weeks and in a study of inhalation doses up to 193 mcg/kg (approximately 8 and 5 times the maximum human daily intranasal dose in adults and children, respectively, based on mcg/m²) in rats for 104 weeks. Ciclesonide was not mutagenic in an Ames test or in a forward mutation assay and was not clastogenic in a human lymphocyte assay or in an *in vitro* micronucleus test. However, ciclesonide was clastogenic in the *in vivo* mouse micronucleus test. The concurrent reference corticosteroid (dexamethasone) in this study showed similar findings. No evidence of impairment of fertility was observed in a reproductive study conducted in male and female rats both dosed orally up to

900 mcg/kg/day (approximately 35 times the maximum human daily intranasal dose in adults based on mcg/m²).

Pregnancy: Teratogenic Effects

Pregnancy Category C

Oral administration of ciclesonide in rats up to 900 mcg/kg (approximately 35 times the maximum human daily intranasal dose in adults based on mcg/m²) produced no teratogenic or other fetal effects. However, subcutaneous administration of ciclesonide in rabbits at 5 mcg/kg (less than the maximum human daily intranasal dose in adults based on mcg/m²) or greater produced fetal toxicity. This included fetal loss, reduced fetal weight, cleft palate, skeletal abnormalities including incomplete ossifications, and skin effects. No toxicity was observed at 1 mcg/kg (less than the maximum human daily intranasal dose based on mcg/m²).

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

Nonteratogenic Effects

Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully monitored.

Nursing Mothers

It is not known if ciclesonide is excreted in human milk. However, other corticosteroids are excreted in human milk. In a study with lactating rats, minimal but detectable levels of ciclesonide were recovered in milk. Caution should be used when OMNARIS Nasal Spray is administered to nursing women.

Pediatric Use

The safety and effectiveness for seasonal and perennial allergic rhinitis in children 12 years of age and older have been established. The efficacy of OMNARIS Nasal Spray in patients 6 to 11 years of age for treatment of the symptoms of seasonal allergic rhinitis is supported by evidence from four adequate and well-controlled studies in adults and adolescents 12 years of age and older with seasonal and perennial allergic rhinitis, and one study in patients 6 to 11 years of age with seasonal allergic rhinitis. The efficacy of OMNARIS Nasal Spray for the treatment of the symptoms of perennial allergic rhinitis in patients 6 to 11 years of age has not been established (see CLINICAL TRIALS: Pediatric Patients Aged 6 to 11 Years). The efficacy of OMNARIS Nasal Spray in children 2 to 5 years of age has not been established. The safety of OMNARIS Nasal Spray in children 2 to 11 years of age was evaluated in 4 controlled clinical studies of 2 to 12 weeks duration (see CLINICAL PHARMACOLOGY: Pharmacodynamics, CLINICAL TRIALS, ADVERSE REACTIONS: Pediatric Patients).

Clinical studies in children less than two years of age have not been conducted. Studies in children under 2 years of age are waived because of local and systemic safety concerns.

Controlled clinical studies have shown that intranasal corticosteroids may cause a reduction in growth velocity in pediatric patients. This effect has been observed in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA)-axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA-axis function. The long-term effects of this reduction in growth velocity associated with intranasal corticosteroids, including the impact on final adult height, are unknown. The potential for “catch-up” growth following discontinuation of treatment with intranasal corticosteroids has not been adequately studied. The growth of pediatric patients receiving intranasal corticosteroids, including OMNARIS Nasal Spray, should be monitored routinely (e.g., via stadiometry). The potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the availability of safe and effective noncorticosteroid treatment alternatives. To minimize the systemic effects of intranasal corticosteroids, each patient should be titrated to the lowest dose that effectively controls his/her symptoms.

Geriatric Use

Clinical studies of OMNARIS Nasal Spray did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Adult and Adolescent Patients Aged 12 Years and Older:

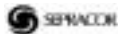
In controlled clinical studies conducted in the US and Canada, a total of 1524 patients ages 12 years and older received treatment with ciclesonide administered intranasally. The overall incidence of adverse events for patients treated with OMNARIS Nasal Spray was comparable to that in patients treated with placebo. Adverse events did not differ appreciably based on age, gender, or race. Approximately 2% of patients treated with OMNARIS Nasal Spray 200 mcg in clinical trials discontinued because of adverse events; this rate was similar for patients treated with placebo. Adverse events, irrespective of drug relationship, that occurred with an incidence of 2% or greater and more frequently with OMNARIS Nasal Spray 200 mcg (N = 546) than with placebo (N = 544) in clinical trials of 2 to 6 weeks in duration included headache (6.0% vs 4.6%), epistaxis (4.9% vs 2.9%), nasopharyngitis (3.7% vs 3.3%), and ear pain (2.2% vs 0.6%). In a 52-week long-term safety trial that included 663 adults and adolescent patients (441 treated with ciclesonide; 227 males and 436 females) with perennial allergic rhinitis, the adverse event profile over the treatment period was similar to the adverse event profile in trials of shorter duration. Adverse events considered likely or definitely related to OMNARIS Nasal Spray that were reported at an incidence of 1% or greater of patients and more commonly in OMNARIS Nasal Spray versus placebo were epistaxis, nasal discomfort, and headache. No patient experienced a nasal septal perforation or nasal ulcer during long-term use of OMNARIS Nasal Spray. While primarily designed to assess the long-term safety of OMNARIS Nasal Spray 200 mcg once daily, this 52-week trial demonstrated greater decreases in total nasal symptom scores with OMNARIS Nasal Spray versus placebo treated patients over the entire treatment period.

Pediatric Patients Aged 6 to 11 Years:

Two controlled clinical studies 2 and 12 weeks in duration were conducted in the US and Canada and included a total of 1282 patients with allergic rhinitis ages 6 to 11 years, of which 913 were treated with OMNARIS (ciclesonide) Nasal Spray 200 mcg, 100 mcg, or 25 mcg daily. The overall incidence of adverse events for patients treated with OMNARIS Nasal Spray was comparable to that in patients treated with placebo. Adverse events did not differ appreciably based on age, gender, or race. In clinical trials, 1.6% and 2.7% of patients treated with OMNARIS Nasal Spray 200 mcg or 100 mcg, respectively, discontinued because of adverse events; these rates were lower than the rate in patients treated with placebo (2.8%). Adverse events, irrespective of drug relationship, that occurred with an incidence of 3% or greater and more frequently with OMNARIS Nasal Spray 200 mcg (N = 380) than with placebo (N = 369) included headache (6.6% vs 5.7%), nasopharyngitis (6.6% vs 5.4%), and pharyngolaryngeal pain (3.4% vs 3.3%).

Pediatric Patients Aged 2 to 5 Years:

Two controlled clinical studies 6 and 12 weeks in duration were conducted in the US and included a total of 258 patients 2 to 5 years of age with perennial allergic rhinitis, of which 183 were treated with OMNARIS Nasal Spray 200 mcg, 100 mcg or 25 mcg daily. The distribution of adverse events was similar to that seen in the 6 to 11 year old children.



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