

Zoster Vaccine Recommended for Age 60 and Up

BY NANCY WALSH
New York Bureau

People aged 60 years and older should receive the herpes zoster vaccine to prevent the development of shingles, the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices recommends.

A single dose of the vaccine can be given to adults 60 years and older even if they have already had an episode of shingles,

which is characterized by the development of blisters and severe pain that can persist for months or even years. The vaccine—made by Merck & Co.—is not indicated to treat acute zoster, to prevent patients with zoster from developing postherpetic neuralgia, or to treat ongoing postherpetic neuralgia. It does not compromise the immunogenicity of trivalent inactivated influenza vaccine when given simultaneously.

The new recommendation, published in

an early-release electronic edition of Morbidity and Mortality Weekly Report, replaces a provisional recommendation made by the CDC's Advisory Committee on Immunization Practices after licensure of the vaccine in 2006 by the Food and Drug Administration. The MMWR report also addresses other aspects of treating herpes zoster, such as oral antiviral agents acyclovir, valacyclovir, and famciclovir, which reduce the severity and duration of acute pain from zoster.

The zoster vaccine is not licensed for persons under age 60 years or for persons of any age who have received varicella vaccine.

Zoster vaccine is contraindicated for persons with a history of anaphylactic reaction to any component of the vaccine, including gelatin and neomycin; persons with primary or acquired immunodeficiency; and pregnant women, although that is not very likely in this age group.

In a phase III, double-blind, placebo-controlled study of 38,546 healthy adults aged 60 years and older with a history of varicella or residency in the United States of 30 years of more, the vaccine reduced the risk of developing zoster by 51% and was 67% effective in preventing postherpetic neuralgia. The mean severity-by-duration of zoster was reduced by 57% in vaccine recipients who developed postherpetic neuralgia. The vaccine's efficacy declined with age: Efficacy against zoster was 18% for persons aged 80 years and older, but efficacy against postherpetic neuralgia was 39%.

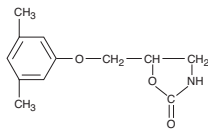
The most common side effects associated with the vaccine are redness, pain, and swelling at the injection site, as well as pruritus and headache.

The risk of developing shingles increases with age, and approximately half of people who live to age 85 will develop the condition.

SKELAXIN® (Metaxalone) Tablets

DESCRIPTION

SKELAXIN® (metaxalone) is available as an 800 mg oval, scored pink tablet. Chemically, metaxalone is 5-[(3,5-dimethylphenoxy)methyl]-2-oxazolidinone. The empirical formula is C₁₁H₁₃NO₂, which corresponds to a molecular weight of 221.25. The structural formula is:



Metaxalone is a white to almost white, odorless crystalline powder freely soluble in chloroform, soluble in methanol and in 96% ethanol, but practically insoluble in ether or water.

Each tablet contains 800 mg metaxalone and the following inactive ingredients: alginate acid, ammonium calcium alginate, B-Rose Liquid, corn starch and magnesium stearate.

CLINICAL PHARMACOLOGY

Mechanism of Action: The mechanism of action of metaxalone in humans has not been established, but may be due to general central nervous system depression. Metaxalone has no direct action on the contractile mechanism of striated muscle, the motor end plate or the nerve fiber.

Pharmacokinetics:

The pharmacokinetics of metaxalone have been evaluated in healthy adult volunteers after single dose administration of SKELAXIN under fasted and fed conditions at doses ranging from 400 mg to 800 mg.

Absorption

Peak plasma concentrations of metaxalone occur approximately 3 hours after a 400 mg oral dose under fasted conditions. Thereafter, metaxalone concentrations decline log-linearly with a terminal half-life of 9.0 ± 4.8 hours. Doubling the dose of SKELAXIN from 400 mg to 800 mg results in a roughly proportional increase in metaxalone exposure as indicated by peak plasma concentrations (C_{max}) and area under the curve (AUC). Dose proportionality at doses above 800 mg has not been studied. The absolute bioavailability of metaxalone is not known.

The single-dose pharmacokinetic parameters of metaxalone in two groups of healthy volunteers are shown in Table 1.

Dose (mg)	C _{max} (ng/mL)	T _{max} (h)	AUC ₀₋₄ (ng·h/mL)	t _{1/2} (h)	CL/F (L/h)
400 ^a	983 (53)	3.3 (35)	7479 (51)	9.0 (53)	68 (50)
800 ^b	1816 (43)	3.0 (39)	15044 (46)	8.0 (58)	66 (51)

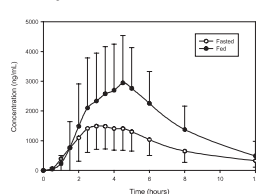
^aSubjects received 1x400 mg tablet under fasted conditions (N=42)
^bSubjects received 2x400 mg tablets under fasted conditions (N=59)

Food Effects

A randomized, two-way, crossover study was conducted in 42 healthy volunteers (31 males, 11 females) administered one 400 mg SKELAXIN tablet under fasted conditions and following a standard high-fat breakfast. Subjects ranged in age from 18 to 48 years (mean age = 23.5 ± 5.7 years). Compared to fasted conditions, the presence of a high fat meal at the time of drug administration increased C_{max} by 177.5% and increased AUC (AUC₀₋₄, AUC_{0-∞}) by 123.5% and 115.4%, respectively. Time-to-peak concentration (T_{max}) was also delayed (4.3 h versus 3.3 h) and terminal half-life was decreased (2.4 h versus 9.0 h) under fed conditions compared to fasted.

In a second food effect study of similar design, two 400 mg SKELAXIN tablets (800 mg) were administered to healthy volunteers (N=59, 37 males, 22 females), ranging in age from 18-50 years (mean age = 25.6 ± 8.7 years). Compared to fasted conditions, the presence of a high fat meal at the time of drug administration increased C_{max} by 193.6% and increased AUC (AUC₀₋₄, AUC_{0-∞}) by 146.4% and 142.2%, respectively. Time-to-peak concentration (T_{max}) was also delayed (4.9 h versus 3.0 h) and terminal half-life was decreased (4.2 h versus 8.0 h) under fed conditions compared to fasted conditions. Similar food effect results were observed in the above study when one SKELAXIN 800 mg tablet was administered in place of two SKELAXIN 400 mg tablets. The increase in metaxalone exposure coinciding with a reduction in half-life may be attributed to more complete absorption of metaxalone in the presence of a high fat meal (Figure 1).

Figure 1. Mean (SD) Concentrations of Metaxalone following an 800 mg Dose, under Fasted and Fed Conditions



Distribution, Metabolism, and Excretion

Although plasma protein binding and absolute bioavailability of metaxalone are not known, the apparent volume of distribution (V/F ~ 800 L) and lipophilicity (log P = 2.42) of metaxalone suggest that the drug is extensively distributed in the tissues. Metaxalone is metabolized by the liver and excreted in the urine as unidentified metabolites.

Pharmacokinetics in Special Populations

Age: The effects of age on the pharmacokinetics of metaxalone were determined following single administration of two 400 mg tablets (800 mg) under fasted and fed conditions. The results were analyzed separately, as well as in combination with the results from three other studies. Using the combined data, the results indicate that the pharmacokinetics of metaxalone are significantly more affected by age under fasted conditions than under fed conditions, with bioavailability under fasted conditions increasing with age.

The bioavailability of metaxalone under fasted and fed conditions in three groups of healthy volunteers of varying age is shown in Table 2.

Age (years)	Younger Volunteers		Older Volunteers	
	Fasted	Fed	Fasted	Fed
N	59	21	21	23
C _{max} (ng/mL)	1816 (43)	3510 (41)	2719 (46)	2915 (55)

T _{max} (h)	3.0		4.9		3.0		8.7		2.6		6.5	
	(39)	(48)	(40)	(91)	(30)	(67)						
AUC ₀₋₄ (ng·h/mL)	14531 (47)	20683 (41)	19836 (40)	20482 (37)	23797 (45)	24340 (48)						
AUC _{0-∞} (ng·h/mL)	15045 (46)	20833 (41)	20490 (39)	20815 (37)	24194 (44)	24704 (47)						

Gender: The effect of gender on the pharmacokinetics of metaxalone was assessed in an open label study, in which 48 healthy adult volunteers (24 males, 24 females) were administered two SKELAXIN 400 mg tablets (800 mg) under fasted conditions. The bioavailability of metaxalone was significantly higher in females compared to males as evidenced by C_{max} (2115 ng/mL versus 1335 ng/mL) and AUC_{0-∞} (17884 ng·h/mL versus 10328 ng·h/mL). The mean half-life was 11.1 hours in females and 7.6 hours in males. The apparent volume of distribution of metaxalone was approximately 22% higher in males than in females, but not significantly different when adjusted for body weight. Similar findings were also seen when the previously described combined dataset was used in the analysis.

Hepatic/Renal Insufficiency: The impact of hepatic and renal disease on the pharmacokinetics of metaxalone has not been determined. In the absence of such information, SKELAXIN should be used with caution in patients with hepatic and/or renal impairment.

INDICATIONS AND USAGE

SKELAXIN (metaxalone) is indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions. The mode of action of this drug has not been clearly identified, but may be related to its sedative properties. Metaxalone does not directly relax tense skeletal muscles in man.

CONTRAINDICATIONS

Known hypersensitivity to any components of this product. Known tendency to drug induced, hemolytic, or other anemias. Significantly impaired renal or hepatic function.

WARNINGS

SKELAXIN may enhance the effects of alcohol and other CNS depressants.

PRECAUTIONS

Metaxalone should be administered with great care to patients with pre-existing liver damage. Serial liver function studies should be performed in these patients.

False-positive Benedict's tests, due to an unknown reducing substance, have been noted. A glucose-specific test will differentiate findings.

Taking SKELAXIN with food may enhance general CNS depression; elderly patients may be especially susceptible to this CNS effect. (See CLINICAL PHARMACOLOGY: Pharmacokinetics and PRECAUTIONS: Information for Patients section).

Information for Patients

SKELAXIN may impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle, especially when used with alcohol or other CNS depressants.

Drug Interactions

SKELAXIN may enhance the effects of alcohol, barbiturates and other CNS depressants.

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of metaxalone has not been determined.

Pregnancy

Reproduction studies in rats have not revealed evidence of impaired fertility or harm to the fetus due to metaxalone. Post marketing experience has not revealed evidence of fetal injury, but such experience cannot exclude the possibility of infrequent or subtle damage to the human fetus. Safe use of metaxalone has not been established with regard to possible adverse effects upon fetal development. Therefore, metaxalone tablets should not be used in women who are or may become pregnant and particularly during early pregnancy unless in the judgement of the physician the potential benefits outweigh the possible hazards.

Nursing Mothers

It is not known whether this drug is secreted in human milk. As a general rule, nursing should not be undertaken while a patient is on a drug since many drugs are excreted in human milk.

Pediatric Use

Safety and effectiveness in children 12 years of age and below have not been established.

ADVERSE REACTIONS

The most frequent reactions to metaxalone include: CNS: drowsiness, dizziness, headache, and nervousness or "irritability";

Digestive: nausea, vomiting, gastrointestinal upset.

Other adverse reactions are:

Immune System: hypersensitivity reaction, rash with or without pruritus;

Hematologic: leukopenia; hemolytic anemia;

Hepatobiliary: jaundice.

Though rare, anaphylactoid reactions have been reported with metaxalone.

OVERDOSAGE

Deaths by deliberate or accidental overdose have occurred with metaxalone, particularly in combination with antidepressants, and have been reported with this class of drug in combination with alcohol.

When determining the LD₅₀ in rats and mice, progressive sedation, hypnosis and finally respiratory failure were noted as the dosage increased. In dogs, no LD₅₀ could be determined as the higher doses produced an emetic action in 15 to 30 minutes.

Treatment - Gastric lavage and supportive therapy. Consultation with a regional poison control center is recommended.

DOSAGE AND ADMINISTRATION

The recommended dose for adults and children over 12 years of age is one 800 mg tablet three to four times a day.

HOW SUPPLIED

SKELAXIN (metaxalone) is available as an 800 mg oval, scored pink tablet inscribed with 8667 on the scored side and "S" on the other. Available in bottles of 100 (NDC 60793-136-01) and in bottles of 500 (NDC 60793-136-05).

Store at Controlled Room Temperature, between 15°C and 30°C (59°F and 86°F).

Rx Only

Prescribing Information as of April 2007.



King Pharmaceuticals

Distributed by: King Pharmaceuticals, Inc., Bristol, TN 37620
Manufactured by: Mallinckrodt Inc., Hobart, NY 13788



www.kingpharm.com www.skelaxin.com

SKELAXIN is a registered trademark of King Pharmaceuticals Research and Development, Inc., a wholly owned subsidiary of King Pharmaceuticals, Inc.

Copyright © 2008 King Pharmaceuticals, Inc.

All rights reserved.

SKE5180

02/2008

Family History Predicts Herpes Zoster Risk

The risk of developing herpes zoster appears to be strongly associated with a family history of the disorder, researchers said.

If further studies confirm this link, people whose family histories put them at risk can be targeted for vaccination, according to Lindsey D. Hicks, a medical student at the University of Texas at Houston, and her associates.

Noting that a recent literature review suggested that a family history of herpes zoster might be predictive but that the issue has not been adequately studied, the investigators conducted a case-control analysis involving 504 patients treated between 1992 and 2005 and 523 well-matched control subjects who never had herpes zoster. Nearly equal proportions of cases and controls (76%) recalled having had primary infection with varicella-zoster virus.

Case patients were about four times more likely than were control subjects to report having a first-degree relative with a history of herpes zoster.

Moreover, the risk of developing herpes zoster rose in a dose-dependent fashion as the number of affected relatives increased. "An odds ratio of 4.5 was calculated for [patients] reporting single [affected] relatives, and an odds ratio of 13.7 was calculated for those reporting multiple [affected] relatives," Ms. Hicks and her associates wrote (Arch. Dermatol. 2008;144:603-8).

—Mary Ann Moon