

Pentacel Vaccine Safety, Efficacy Data Mounting

BY SHERRY BOSCHERT
San Francisco Bureau

SAN FRANCISCO — Two phase II clinical studies of a combination vaccine suggest that it is safe and immunogenic, investigators reported in poster presentations at the annual meeting of the Infectious Diseases Society of America.

An open study of 3,022 healthy infants found comparable immunogenicity and safety results among four lots of the Pen-

tacel vaccine, which is used to immunize against diphtheria, tetanus, pertussis, polio, and *Haemophilus influenzae* type b (Hib), reported Kathryn M. Edwards, M.D.

Seroresponse and seroprotection rates were immunogenic with vaccine from all four lots despite coadministration with pneumococcal conjugate (Prevnar) vaccine. In some previous reports, Prevnar vaccine was associated with interference with coadministered pertussis or Hib vaccines, said Dr. Edwards, professor of pe-

diatrics at Vanderbilt University, Nashville, Tenn. She has received funding from Sanofi and from Aventis-Sofitel, part of the Sanofi-Aventis Group, which makes the vaccine. Her associates in the study were employed by Sanofi Pasteur Inc.

Sanofi-Aventis has applied to the Food and Drug Administration for licensing to market Pentacel in the United States. If approved, the four-dose series of Pentacel could reduce the number of recommended childhood vaccine injections by two.

Pentacel is licensed for pediatric use in nine countries.

In the current study, the largest single study of Pentacel vaccine in the United States, healthy infants at 23 clinical centers received concomitant Pentacel and Prevnar vaccines at 2, 4, and 6 months of age. They previously had received hepatitis B vaccine, with second and third doses of that vaccine given at 2 and 6 months of age.

Systemic reactions within 3 days of Pentacel vaccination included fever in 11%-20% of infants, fussiness in 60%-71%, and crying in 35%-45%. Two of three serious adverse events that were temporally associated with vaccination were considered to be possibly related to the vaccine.

One 2-month-old developed a hypotonic hyporesponsive episode (HHE) that began 2 hours after the first dose and lasted 8 hours. The infant recovered without treatment, had no sequelae, and received no further doses. This is the first episode



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DR. EDWARDS

of HHE reported in more than 16,000 doses of Pentacel administered so far, Dr. Edwards noted. Another 2-month-old had about eight afebrile seizure episodes 3 days after the first dose, each lasting less than 1 minute. The child was hospitalized for a day and was discharged after normal brain imaging and EEG results. Exam results 2 weeks later were normal. A febrile seizure in a third child with acute otitis media was considered unrelated to the vaccine.

A separate study presented at the meeting extended previous results from a randomized, controlled, multicenter study that found comparable safety and immunogenicity among three doses of Pentacel vaccine; individual administration of vaccines for polio and Hib; and a combination vaccine for diphtheria, tetanus, and acellular pertussis (DTaP).

The current data looked at a fourth dose of Pentacel vaccine in 430 infants or separate administration of the Hib and DTaP vaccines in 419 infants at 15 months of age. The protocol criteria were met by 371 in the Pentacel group and 349 in the control group. The vaccines were coadministered with three doses of Prevnar vaccine and two doses of hepatitis B vaccine in the first part of the study.

Immune responses to each antigen remained comparable between the Pentacel vaccine group and the control group after the 15-month doses in the second part of the study, reported Fernando Noriega, M.D., of Sanofi Pasteur, Swiftwater, Penn., and his associates.

There were no serious adverse events related to the vaccine and no reports of HHE. The investigators found no clinically relevant differences between the safety profiles of the Pentacel vaccine and the DTaP vaccine, Dr. Noriega said.

Axid® (nizatidine) Oral Solution

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

Contraindication: Axid Oral Solution is contraindicated in patients with known hypersensitivity to the drug. Because cross-sensitivity in this class of compounds has been observed, H₂-receptor antagonists, including nizatidine, should not be administered to patients with a history of hypersensitivity to other H₂-receptor antagonists.

Precautions: *General*—1. Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy.

2. Because nizatidine is excreted primarily by the kidney, dosage should be reduced in patients with moderate to severe renal insufficiency (see Dosage and Administration).

3. Pharmacokinetic studies in patients with hepatorenal syndrome have not been done. Part of the dose of nizatidine is metabolized in the liver. In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects.

Laboratory Tests—False-positive tests for urobilinogen with Multistix® may occur during therapy with nizatidine.

Drug Interactions—No interactions have been observed between nizatidine and theophylline, chlorthalidone, lorazepam, lidocaine, phenytoin, and warfarin. Nizatidine does not inhibit the cytochrome P-450-linked drug-metabolizing enzyme system; therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3,900 mg) of aspirin daily, increases in serum salicylate levels were seen when nizatidine, 150 mg b.i.d., was administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility—A 2-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 13 times the recommended human dose based on body surface area) showed no evidence of a carcinogenic effect. There was a dose-related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a 2-year study in mice, there was no evidence of a carcinogenic effect in male mice; although hyperplastic nodules of the liver were increased in the high-dose males as compared with placebo. Female mice given the high dose of nizatidine (2,000 mg/kg/day, about 27 times the recommended human dose based on body surface area) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high-dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement as compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 5 times the recommended human dose based on body surface area), and a negative mutagenicity battery are not considered evidence of a carcinogenic potential for nizatidine.

Nizatidine was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, mouse lymphoma assay, chromosome aberration tests, and a micronucleus test.

In a 2-generation, perinatal and postnatal fertility study in rats, doses of nizatidine up to 650 mg/kg/day (about 17.5 times the recommended human dose based on body surface area) produced no adverse effects on the reproductive performance of parental animals or their progeny.

Pregnancy—Teratogenic Effects—Pregnancy Category B—Oral reproduction studies in pregnant rats at doses up to 1500 mg/kg/day (about 40.5 times the recommended human dose based on body surface area) and in pregnant rabbits at doses up to 275 mg/kg/day (about 14.6 times the recommended human dose based on body surface area) have revealed no evidence of impaired fertility or harm to the fetus due to nizatidine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers—Studies conducted in lactating women have shown that 0.1% of the administered oral dose of nizatidine is secreted in human milk in proportion to plasma concentrations. Because of the growth depression in pups reared by lactating rats treated with nizatidine, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use—Effectiveness in pediatric patients <12 years of age has not been established. Use of nizatidine in pediatric patients from 12 to 18 years of age is supported by evidence from published pediatric literature, adequate and well-controlled published studies in adults, and by the following adequate and well-controlled studies in pediatric patients: (see DOSAGE AND ADMINISTRATION)

Clinical Trials (Pediatric). In randomized studies, nizatidine was administered to pediatric patients for up to eight weeks, using age appropriate formulations. A total of 230 pediatric patients from 2 to 18 years of age were administered nizatidine at a dose of either 2.5 mg/kg b.i.d., or 5.0 mg/kg b.i.d., (patients 12 years and under) or 150 mg b.i.d. (12 to 18 years). Patients were required to have either symptomatic, clinically suspected or endoscopically diagnosed GERD with age-relevant symptoms. In patients 2 to 18 years of age, nizatidine was found generally safe and well-tolerated. In these studies in patients 12 years and older, nizatidine was found to reduce the severity and frequency of GERD symptoms, improve physical well-being, and reduce the frequency of supplemental antacid consumption. No efficacy in pediatric patients <12 years of age has been established. Clinical studies in patients 2 to 12 years of age with GERD, demonstrated no difference in either symptom improvements or healing rates between nizatidine and placebo or between different doses of nizatidine.

Geriatric Use—Of the 955 patients in clinical studies who were treated with nizatidine, 337 (35.3%) were 65 and older. No overall differences in safety or effectiveness were observed between these and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see Dosage and Administration).

Adverse Reactions in Adults: Worldwide, controlled clinical trials of nizatidine included over 6,000 patients given nizatidine in studies of varying durations. Placebo-controlled trials in the United States and Canada included over 2,600 patients given nizatidine and over 1,700 given placebo. Among the adverse events in these placebo-controlled trials, anemia (0.2% vs 0%) and urticaria (0.5% vs 0.1%) were significantly more common in the nizatidine group.

Incidence in Placebo-Controlled Clinical Trials in the United States and Canada—Table 7 lists adverse events that occurred at a frequency of 1% or more among nizatidine-treated patients who participated in placebo-controlled trials. The cited figures provide some basis for estimating the relative contribution of drug and non-drug factors to the side-effect incidence rate in the population studied.

Table 7. Incidence of Treatment-Emergent Adverse Events in Placebo-Controlled Clinical Trials in the United States and Canada					
Body System/ Adverse Event*	Percentage of Patients Reporting Event		Body System/ Adverse Event*	Percentage of Patients Reporting Event	
	Nizatidine (N=2,694)	Placebo (N=1,729)		Nizatidine (N=2,694)	Placebo (N=1,729)
Body as a Whole			Nervous		
Headache	16.6	15.6	Dizziness	4.6	3.8
Pain	4.2	3.8	Insomnia	2.7	3.4
Asthenia	3.1	2.9	Abnormal dreams	1.9	1.9
Chest pain	2.3	2.1	Somnolence	1.9	1.6
Infection	1.7	1.1	Anxiety	1.8	1.4
Injury, accident	1.2	0.9	Nervousness	1.1	0.8
Digestive			Respiratory		
Diarrhea	7.2	6.9	Rhinitis	9.8	9.6
Dry mouth	1.4	1.3	Pharyngitis	3.3	3.1
Tooth disorder	1.0	0.8	Sinusitis	2.4	2.1
Musculoskeletal			Cough, increased		
Myalgia	1.7	1.5		2.0	2.0
			Skin and Appendages		
			Rash	1.9	2.1
			Pruritus	1.7	1.3
			Special Senses		
			Amblyopia	1.0	0.9

*Events reported by at least 1% of nizatidine-treated patients are included.

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A variety of less common events were also reported; it was not possible to determine whether these were caused by nizatidine.

Hepatic—Hepatocellular injury, evidenced by elevated liver enzyme tests (SGOT [AST], SGPT [ALT], or alkaline phosphatase), occurred in some patients and was possibly or probably related to nizatidine. In some cases, there was marked elevation of SGOT, SGPT enzymes (greater than 500 IU/L) and, in a single instance, SGPT was greater than 2,000 IU/L. The overall rate of occurrences of elevated liver enzymes and elevations to 3 times the upper limit of normal, however, did not significantly differ from the rate of liver enzyme abnormalities in placebo-treated patients. All abnormalities were reversible after discontinuation of nizatidine. Since market introduction, hepatitis and jaundice have been reported. Rare cases of cholestatic or mixed hepatocellular and cholestatic injury with jaundice have been reported with reversal of the abnormalities after discontinuation of nizatidine.

Cardiovascular—In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in 2 individuals administered nizatidine and in 3 untreated subjects.

CNS—Rare cases of reversible mental confusion have been reported.

Endocrine—Clinical pharmacology studies and controlled clinical trials showed no evidence of antiandrogenic activity due to nizatidine. Impotence and decreased libido were reported with similar frequency by patients who received nizatidine and by those given placebo. Rare reports of gynecomastia occurred.

Hematologic—Anemia was reported significantly more frequently in nizatidine- than in placebo-treated patients. Fatal thrombocytopenia was reported in a patient who was treated with nizatidine and another H₂-receptor antagonist. On previous occasions, this patient had experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

Integumental—Sweating and urticaria were reported significantly more frequently in nizatidine- than in placebo-treated patients. Rash and exfoliative dermatitis were also reported. Vasculitis has been reported rarely.

Hypersensitivity—As with other H₂-receptor antagonists, rare cases of anaphylaxis following administration of nizatidine have been reported. Rare episodes of hypersensitivity reactions (eg, bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.

Body as a Whole—Serum sickness-like reactions have occurred rarely in conjunction with nizatidine use.

Genitourinary—Reports of impotence have occurred.

Other—Hyperuricemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever, and nausea related to nizatidine administration have been reported.

Adverse Reactions (Pediatric): In controlled clinical trials in pediatric patients (age 2 to 18 years), nizatidine was found to be generally safe and well tolerated. The principal adverse experiences (>5%) were pyrexia, nasopharyngitis, diarrhea, vomiting, irritability, nasal congestion and cough. Most adverse events were mild or moderate in severity. Mild elevations in serum transaminase (1-2 x ULN) were noted in some patients. One subject experienced a seizure by EEG diagnosis after taking Axid Oral Solution 2.5 mg/kg b.i.d. for 23 days. The adverse reactions reported for nizatidine may also occur with Axid Oral Solution.

Overdosage: Overdoses of nizatidine have been reported rarely. The following is provided to serve as a guide should such an overdose be encountered.

Signs and Symptoms—There is little clinical experience with overdosage of nizatidine in humans. Test animals that received large doses of nizatidine have exhibited cholinergic-type effects, including lacrimation, salivation, emesis, miosis, and diarrhea. Single oral doses of 800 mg/kg in dogs and of 1,200 mg/kg in monkeys were not lethal. Intravenous median lethal doses in the rat and mouse were 301 mg/kg and 232 mg/kg, respectively.

In the two 8-week pediatric exposure trials of nizatidine in 256 pediatric patients, there were no cases of deliberate overdosage. In one study of nizatidine 10 mg/kg/day, drug compliance rates up to 7.5% above 100% compliance were not associated with clinically significant adverse events.

Treatment—To obtain up-to-date information about the treatment of overdosage, a good resource is your certified Regional Poison Control Center. Telephone numbers of certified Poison Control Centers are listed in the *Physicians' Desk Reference (PDR)*. In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

If overdosage occurs, use of activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. The ability of hemodialysis to remove nizatidine from the body has not been conclusively demonstrated; however, due to its large volume of distribution, nizatidine is not expected to be efficiently removed from the body by this method.

Dosage and Administration:

Active Duodenal Ulcer—The recommended oral dosage for adults is 300 mg once daily at bedtime.

An alternative dosage regimen is 150 mg twice daily.

Maintenance of Healed Duodenal Ulcer—The recommended oral dosage for adults is 150 mg once daily at bedtime.

Gastroesophageal Reflux Disease—The recommended oral dosage in adults for the treatment of erosions, ulcerations, and associated heartburn is 150 mg twice daily.

Active Benign Gastric Ulcer—The recommended oral dosage is 300 mg given either as 150 mg twice daily or 300 mg once daily at bedtime. Prior to treatment, care should be taken to exclude the possibility of malignant gastric ulceration.

Each mL of Axid Oral Solution contains 15 mg of nizatidine. In adults, Axid Oral Solution may be substituted for any of the above indications using equivalent doses of the oral solution.

Pediatric Dosing—Each mL of oral solution contains 15 mg of nizatidine. Axid Oral Solution is indicated for pediatric patients 12 years of age or older. For pediatric patients 12 years of age and older, the dosage of nizatidine is 150 mg b.i.d. (2 tsp, b.i.d.)

The following dosage recommendations are provided:

Erosive Esophagitis—For pediatric patients 12 years or older, the dosage is 150 mg b.i.d. (300 mg/d). The maximum daily dose for nizatidine PO is 300 mg/d. The dosing duration may be up to eight weeks.

Gastroesophageal Reflux Disease—For pediatric patients 12 years or older, the dosage is 150 mg b.i.d. (300 mg/d). The maximum daily dose for nizatidine PO is 300 mg/d. The dosing duration may be up to eight weeks.

Dosage Adjustment for Patients With Moderate to Severe Renal Insufficiency—The dose for patients with renal dysfunction should be reduced as follows:

Active Duodenal Ulcer, GERD, and Benign Gastric Ulcer		
Creatinine Clearance	Dose	
20-50 mL/min	150 mg daily	
<20 mL/min	150 mg every other day	
Maintenance Therapy		
Creatinine Clearance	Dose	
20-50 mL/min	150 mg every other day	
<20 mL/min	150 mg every 3 days	

Some elderly patients may have creatinine clearances of less than 50 mL/min, and, based on pharmacokinetic data in patients with renal impairment, the dose for such patients should be reduced accordingly. The clinical effects of this dosage reduction in patients with renal failure have not been evaluated.

Based on the pharmacokinetic data in elderly patients with renal impairment, pediatric patients with creatinine clearances less than 50 mL/min should have their dose of nizatidine reduced accordingly. The clinical effects of this dose reduction in pediatric patients with renal failure have not been evaluated.

How Supplied:

Axid (nizatidine) Oral Solution 15 mg/mL is formulated as a clear, yellow, oral solution with bubble gum flavor, available as:

Bottles of 480 mL (16 fl. oz.)—NDC# 52268-147-62

Store at 25°C (77°F); excursions permitted to 15° - 30°C (59° - 86°F) [see USP Controlled Room Temperature] and dispense in tight, light-resistant container.

LABORATORIES INC
Braintree

Manufactured for:
Braintree Laboratories, Inc.
Braintree, MA 02185

By:
Lyne Laboratories, Inc.
Brockton, MA 02301, USA

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Address Medical Inquiries to:
Braintree Laboratories, Inc.
P.O. Box 850929
Braintree, MA 02185