

19A Serotype Dominant Among Infection Isolates

BY DOUG BRUNK
San Diego Bureau

SAN DIEGO — Serotype 19A is the most common serotype isolated from children’s invasive pneumococcal infections, results from a national multicenter study suggest.

The finding comes from the United States Pediatric Multicenter Pneumococcal Surveillance Study Group, a network of eight children’s hospitals that has been

identifying patients with systemic pneumococcal infections since 1993. The researchers send the isolates to a central laboratory for serotyping and complete a standardized case report form that includes demographic and clinical information, including the number of 7-valent pneumococcal conjugate vaccinations (PCV7) the child has received.

At the annual meeting of the Infectious Diseases Society of America, Dr. Sheldon L. Kaplan reported on 1,234 isolates col-

lected between April 1, 2000, and Dec. 31, 2006. Ages of patients ranged from 0 to 20 years, but most infections occurred in the first 5 years of life. Serotype 19A accounted for 19% of all nonvaccine serotype isolates in 2000, 22% in 2001, 18% in 2002, 23% in 2003, 39% in 2004, 34% in 2005, and 49% in 2006.

Serotype 19A has been the most common nonvaccine serotype each year since 2003. In 2005 and 2006 combined, the next most common nonvaccine serotypes

were 1 (21 cases), 3 (14 cases), 33, 15, and 7 (13 cases each), and 6A (11 cases).

No deaths were reported associated with pneumococcal infections in 2006. “The number of invasive infections reached its lowest point in 2004 and then increased 13% in 2005 and another 5% in 2006,” Dr. Kaplan, chief of the infectious disease service at Texas Children’s Hospital, Houston, noted in a later interview. “Nevertheless, the number of cases annually was still 60% less than seen each year before the pneumococcal conjugate vaccine was licensed for routine administration to infants.”

The most common type of infection among children with serotype 19A was bacteremia, followed by pneumonia, bacterial meningitis, and other infections.

Continued surveillance of invasive pneumococcal infections was predicted to remain necessary following the inclusion of serotype 19A.

When the researchers applied the 2007 breakpoints for minimum inhibitory concentration interpretations, they found that 28% of 19A isolates in 2006 were susceptible to penicillin, 34% were immediately susceptible to penicillin, and 37% were resistant to penicillin.

Dr. Kaplan, who is also a professor of pediatrics at Baylor College of Medicine, predicted that the percentage of isolates resistant to penicillin “will go down dramatically” when the Clinical and Laboratory Standards Institute publishes new *Streptococcus pneumoniae* penicillin breakpoints for nonmeningeal pneumococcal isolates in 2008. He concluded that continued surveillance of invasive pneumococcal infections “will remain necessary following the inclusion of serotype 19A and other serotypes.”

The pneumococcal surveillance group includes clinicians from Texas Children’s Hospital, Houston; Children’s Hospital of Pittsburgh; Children’s Hospital San Diego; Columbus (Ohio) Children’s Hospital; Children’s Memorial Hospital, Chicago; Arkansas Children’s Hospital, Little Rock; Brenner Children’s Hospital, Wake Forest, N.C.; and Children’s Hospital Los Angeles.

Dr. Kaplan disclosed that he has received research grants from Roche and Wyeth Pharmaceuticals. ■

VERBATIM

With some thought and planning, even the busiest pediatrician can fit in continuing education. Taking advantage of the many opportunities available ... can be intellectually and professionally rewarding.

Dr. Lee Savio Beers, p. 34

Brief Summary of Prescribing Information
(Nos. 1541, 1543, 1544, 3046, 7309, 7311)
03-5530-R25-Brl2, Rev. September 2006

PREVACID® (lansoprazole)
Delayed-Release Capsules
PREVACID® (lansoprazole)
For Delayed-Release Oral Suspension
PREVACID® SoluTab™ (lansoprazole)
Delayed-Release Orally Disintegrating Tablets

R only

Indications include:

Short-Term Treatment of Active Duodenal Ulcer
PREVACID is indicated for short-term treatment (for 4 weeks) for healing and symptom relief of active duodenal ulcer.

Maintenance of Healed Duodenal Ulcers
PREVACID is indicated to maintain healing of duodenal ulcers. Controlled studies do not extend beyond 12 months.

Short-Term Treatment of Active Benign Gastric Ulcer
PREVACID is indicated for short-term treatment (up to 8 weeks) for healing and symptom relief of active benign gastric ulcer.

Healing of NSAID-Associated Gastric Ulcer
PREVACID is indicated for the treatment of NSAID-associated gastric ulcer in patients who continue NSAID use. Controlled studies did not extend beyond 8 weeks.

Risk Reduction of NSAID-Associated Gastric Ulcer
PREVACID is indicated for reducing the risk of NSAID-associated gastric ulcers in patients with a history of a documented gastric ulcer who require the use of an NSAID. Controlled studies did not extend beyond 12 weeks.

Gastroesophageal Reflux Disease (GERD)
Short-Term Treatment of Symptomatic GERD
PREVACID is indicated for the treatment of heartburn and other symptoms associated with GERD.

Short-Term Treatment of Erosive Esophagitis
PREVACID is indicated for short-term treatment (up to 8 weeks) for healing and symptom relief of all grades of erosive esophagitis.

For patients who do not heal with PREVACID for 8 weeks (5-10%), it may be helpful to give an additional 8 weeks of treatment.

If there is a recurrence of erosive esophagitis an additional 8-week course of PREVACID may be considered.

Maintenance of Healing of Erosive Esophagitis
PREVACID is indicated to maintain healing of erosive esophagitis. Controlled studies did not extend beyond 12 months.

Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome
PREVACID is indicated for the long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome.

CONTRAINDICATIONS
PREVACID is contraindicated in patients with known severe hypersensitivity to any component of the formulation of PREVACID.

PRECAUTIONS
General
Symptomatic response to therapy with lansoprazole does not preclude the presence of gastric malignancy.

Information for Patients
PREVACID is available as a capsule, orally disintegrating tablet and oral suspension, and is available in 15 mg and 30 mg strengths. Directions for use specific to the route and available methods of administration for each of these dosage forms is available in the complete prescribing information. PREVACID should be taken before eating. PREVACID products SHOULD NOT BE CRUSHED OR CHEWED.

Phenylketonurics: Contains Phenylalanine 2.5 mg per 15 mg Tablet and 5.1 mg per 30 mg Tablet.

Drug Interactions
Lansoprazole is metabolized through the cytochrome P₄₅₀ system, specifically through the CYP3A and CYP2C19 isozymes. Studies have shown that lansoprazole does not have clinically significant interactions with other drugs metabolized by the cytochrome P₄₅₀ system, such as warfarin, antipyrine, indomethacin, ibuprofen, phenytoin, propranolol, prednisone, diltiazem, or clarithromycin in healthy subjects. These compounds are metabolized through various cytochrome P₄₅₀ isozymes including CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A. When lansoprazole was administered concomitantly with theophylline (CYP1A2, CYP3A), a minor increase (10%) in the clearance of theophylline was seen. Because of the small magnitude and the direction of the effect on theophylline clearance, this interaction is unlikely to be of clinical concern. Nonetheless, individual patients may require additional titration of their theophylline dosage when lansoprazole is started or stopped to ensure clinically effective blood levels.

In a study of healthy subjects neither the pharmacokinetics of warfarin enantiomers nor prothrombin time were affected following single or multiple 60 mg doses of lansoprazole. However, there have been reports of increased International Normalized Ratio (INR) and prothrombin time in patients receiving proton pump inhibitors, including lansoprazole, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.

In an open-label, single-arm, eight-day, pharmacokinetic study of 28 adult rheumatoid arthritis patients (who required the chronic use of 7.5 to 15 mg of methotrexate given weekly), administration of 7 days of naproxen 500 mg BID and lansoprazole 30 mg daily had no effect on the pharmacokinetics of methotrexate and 7-hydroxymethotrexate. While this study was not designed to assess the safety of this combination of drugs, no major adverse events were noted.

Lansoprazole has also been shown to have no clinically significant interaction with amoxicillin.

In a single-dose crossover study examining lansoprazole 30 mg and omeprazole 20 mg each administered alone and concomitantly with sucralfate 1 gram, absorption of the proton pump inhibitors was delayed and their bioavailability was reduced by 17% and 16%, respectively, when administered concomitantly with sucralfate. Therefore, proton pump inhibitors should be taken at least 30 minutes prior to sucralfate. In clinical

trials, antacids were administered concomitantly with PREVACID and there was no evidence of a change in the efficacy of PREVACID.

Lansoprazole causes a profound and long-lasting inhibition of gastric acid secretion; therefore, it is theoretically possible that lansoprazole may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (e.g., ketoconazole, ampicillin esters, iron salts, digoxin).

Carcinogenesis, Mutagenesis, Impairment of Fertility
In two 24-month carcinogenicity studies, Sprague-Dawley rats were treated with oral lansoprazole doses of 5 to 150 mg/kg/day – about 1 to 40 times the exposure on a body surface (mg/m²) basis, of a 50-kg person of average height [1.46 m² body surface area (BSA)] given the recommended human dose of 30 mg/day (22.2 mg/m²). Lansoprazole produced dose-related gastric enterochromaffin-like (ECL) cell hyperplasia and ECL cell carcinoids in both male and female rats. It also increased the incidence of intestinal metaplasia of the gastric epithelium in both sexes. In male rats, lansoprazole produced a dose-related increase of testicular interstitial cell adenomas. The incidence of these adenomas in rats receiving doses of 15 to 150 mg/kg/day (4 to 40 times the recommended human dose based on BSA) exceeded the low background incidence (range = 1.4 to 10%) for this strain of rat. In addition, in a one-year toxicity study, testicular interstitial cell adenoma occurred in 1 of 30 rats treated with 50 mg/kg/day of lansoprazole (13 times the recommended human dose based on BSA).

In a 24-month carcinogenicity study, CD-1 mice were treated with oral lansoprazole doses of 15 to 600 mg/kg/day, 2 to 80 times the recommended human dose based on BSA. Lansoprazole produced a dose-related increased incidence of gastric ECL cell hyperplasia. It also produced an increased incidence of liver tumors (hepatocellular adenoma plus carcinoma). The tumor incidences in male mice treated with 300 and 600 mg/kg/day (40 to 80 times the recommended human dose based on BSA) and female mice treated with 150 to 600 mg/kg/day (20 to 80 times the recommended human dose based on BSA) exceeded the ranges of background incidences in historical controls for this strain of mice. Lansoprazole treatment produced adenoma of rete testis in male mice receiving 75 to 600 mg/kg/day (10 to 80 times the recommended human dose based on BSA).

Lansoprazole was not genotoxic in the Ames test, the *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) test, the *in vivo* mouse micronucleus test, or the rat bone marrow cell chromosomal aberration test. It was positive in *in vitro* human lymphocyte chromosomal aberration assays.

Lansoprazole at oral doses up to 150 mg/kg/day (40 times the recommended human dose based on BSA) was found to have no effect on fertility and reproductive performance of male and female rats.

Pregnancy: Reproductive Effects.
Pregnancy Category B

Lansoprazole
Teratology studies have been performed in pregnant rats at oral lansoprazole doses up to 150 mg/kg/day (40 times the recommended human dose based on BSA) and pregnant rabbits at oral lansoprazole doses up to 30 mg/kg/day (16 times the recommended human dose based on BSA) and have revealed no evidence of impaired fertility or harm to the fetus due to lansoprazole.

There are, however, no adequate or 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
Lansoprazole or its metabolites are excreted in the milk of rats. It is not known whether lansoprazole is excreted in human milk. Because many drugs are excreted in human milk, because of the potential for serious adverse reactions in nursing infants from lansoprazole, and because of the potential for tumorigenicity shown for lansoprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue lansoprazole, taking into account the importance of lansoprazole to the mother.

Pediatric Use
The safety and effectiveness of PREVACID have been established in pediatric patients 1 to 17 years of age for short-term treatment of symptomatic GERD and erosive esophagitis. Use of PREVACID in this population is supported by evidence from adequate and well-controlled studies of PREVACID in adults with additional clinical, pharmacokinetic, and pharmacodynamic studies performed in pediatric patients. The adverse events profile in pediatric patients is similar to that of adults. There were no adverse events reported in U.S. clinical studies that were not previously observed in adults. The safety and effectiveness of PREVACID in patients less than 1 year of age have not been established.

1 to 11 years of age
The pediatric safety of PREVACID Delayed-Release Capsules has been assessed in 66 pediatric patients aged 1 to 11 years of age. Of the 66 patients with GERD 85% (56/66) took PREVACID for 8 weeks and 15% (10/66) took it for 12 weeks.

The most frequently reported (2 or more patients) treatment-related adverse events in patients 1 to 11 years of age (N=66) were constipation (5%) and headache (3%).

12 to 17 years of age
The safety of PREVACID Delayed-Release Capsules has been assessed in these 87 adolescent patients. Of the 87 adolescent patients with GERD, 6% (5/87) took PREVACID for less than 6 weeks, 93% (81/87) for 6-10 weeks, and 1% (1/87) for greater than 10 weeks.

The most frequently reported (at least 3%) treatment-related adverse events in these patients were headache (7%), abdominal pain (5%), nausea (3%) and dizziness (3%). Treatment-related dizziness, reported in this package insert as occurring in less than 1% of adult patients, was reported in this study by 3 adolescent patients with nonerosive GERD, who had dizziness concurrently with other events (such as migraine, dyspnea, and vomiting).

Use in Women
Over 4,000 women were treated with PREVACID. Ulcer healing rates in females were similar to those in males. The incidence rates of adverse events in females were similar to those seen in males.

Use in Geriatric Patients
The incidence rates of PREVACID-associated adverse events and laboratory test abnormalities are similar to those seen in younger patients. For geriatric patients, dosage and administration of PREVACID need not be altered.

ADVERSE REACTIONS
Clinical
Worldwide, over 10,000 patients have been treated with PREVACID in Phase 2 or Phase 3 clinical trials involving various dosages and durations of treatment. The adverse reaction profiles for PREVACID Delayed-Release Capsules and PREVACID for Delayed-Release Oral Suspension are similar. In general, PREVACID treatment has been well-tolerated in both short-term and long-term trials.

The following adverse events were reported by the treating physician to have a possible or probable relationship to drug in 1% or more of PREVACID-treated patients and occurred at a greater rate in

PREVACID-treated patients than placebo-treated patients. The incidence of the most common possibly or probably treatment-related adverse events with PREVACID in short-term, placebo-controlled studies were abdominal pain (2.1%), constipation (1.0%), diarrhea (3.8%), and nausea (1.3%). Results for placebo for these same events were 1.2%, 0.4%, 2.3%, and 1.2% respectively. Headache was also seen at greater than 1% incidence but was more common on placebo. The incidence of diarrhea was similar between patients who received placebo and patients who received 15 mg and 30 mg of PREVACID, but higher in the patients who received 60 mg of PREVACID (2.9%, 1.4%, 4.2%, and 7.4%, respectively).

The most commonly reported possibly or probably treatment-related adverse event during maintenance therapy was diarrhea.

In the risk reduction study of PREVACID for NSAID-associated gastric ulcers, the incidence of diarrhea for patients treated with PREVACID, misoprostol, and placebo was 5%, 22%, and 3%, respectively.

Additional adverse experiences occurring in less than 1% of patients or subjects who received PREVACID in domestic trials are shown below:

Body as a Whole – abdomen enlarged, allergic reaction, asthenia, back pain, candidiasis, carcinoma, chest pain (not otherwise specified), chills, edema, fever, flu syndrome, halitosis, infection (not otherwise specified), malaise, neck pain, neck rigidity, pain, pelvic pain, Cardiovacular System – angina, arrhythmia, bradycardia, cerebrovascular accident/cerebral infarction, hypertension/hypotension, migraine, myocardial infarction, palpitations, shock (circulatory failure), syncope, tachycardia, vasodilation; *Digestive System* – abnormal stools, anorexia, bezoar, cardiospasm, cholelithiasis, colitis, dry mouth, dyspepsia, dysphagia, enteritis, eructation, esophageal stenosis, esophageal ulcer, esophagitis, fecal discoloration, flatulence, gastric nodules/fundic gland polyps, gastritis, gastroenteritis, gastrointestinal anomaly, gastrointestinal disorder, gastrointestinal hemorrhage, glossitis, gum hemorrhage, hematemesis, increased appetite, increased salivation, melena, mouth ulceration, nausea and vomiting, nausea and vomiting and diarrhea, oral moniliasis, rectal disorder, rectal hemorrhage, stomatitis, tenesmus, thirst, tongue disorder, ulcerative colitis, ulcerative stomatitis; *Endocrine System* – diabetes mellitus, goiter, hypothyroidism; *Hemic and Lymphatic System* – anemia, hemolysis, lymphadenopathy; *Metabolic and Nutritional Disorders* – gout, dehydration, hyperglycemia/hypoglycemia, peripheral edema, weight gain/loss; *Musculoskeletal System* – arthralgia, arthritis, bone disorder, joint disorder, leg cramps, musculoskeletal pain, myalgia, myasthenia, synovitis; *Nervous System* – abnormal dreams, agitation, amnesia, anxiety, apathy, confusion, convulsion, depersonalization, depression, diplopia, dizziness, emotional lability, hallucinations, hemiplegia, hostility aggravated, hyperkinesia, hypertension, hyposthesia, insomnia, libido decreased/increased, nervousness, neurosis, paresthesia, sleep disorder, somnolence, thinking abnormality, tremor, vertigo; *Respiratory System* – asthma, bronchitis, cough increased, dyspnea, epistaxis, hemoptysis, hiccup, laryngeal neoplasia, pharyngitis, pleural disorder, pneumonia, respiratory disorder, upper respiratory inflammation/infection, rhinitis, sinusitis, stridor; *Skin and Appendages* – acne, alopecia, contact dermatitis, dry skin, fixed eruption, hair disorder, maculopapular rash, nail disorder, pruritus, rash, skin carcinoma, skin disorder, sweating, urticaria; *Special Senses* – abnormal vision, blurred vision, conjunctivitis, deafness, dry eyes, ear disorder, eye pain, otitis media, parosmia, photophobia, retinal degeneration, taste loss, taste perversion, tinnitus, visual field defect; *Urogenital System* – abnormal menses, breast enlargement, breast pain, breast tenderness, dysmenorrhea, dysuria, gynecomastia, impotence, kidney calculus, kidney pain, leukorrhea, menorrhagia, menstrual disorder, penis disorder, polyuria, testis disorder, urethral pain, urinary frequency, urinary tract infection, urinary urgency, urination impaired, vaginitis.

Postmarketing
Additional adverse experiences have been reported since PREVACID has been marketed. The majority of these cases are foreign-sourced and a relationship to PREVACID has not been established. Because these events were reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events are listed below by COSTART body system.

Body as a Whole – anaphylactic/anaphylactoid reactions; *Digestive System* – hepatotoxicity, pancreatitis, vomiting; *Hemic and Lymphatic System* – agranulocytosis, aplastic anemia, hemolytic anemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia, and thrombotic thrombocytopenic purpura; *Musculoskeletal System* – myositis; *Skin and Appendages* – severe dermatologic reactions including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (some fatal); *Special Senses* – speech disorder; *Urogenital System* – interstitial nephritis, urinary retention.

Laboratory Values
The following changes in laboratory parameters in patients who received PREVACID were reported as adverse events:
Abnormal liver function tests, increased SGOT (AST), increased SGPT (ALT), increased creatinine, increased alkaline phosphatase, increased globulins, increased GGT, increased/decreased/abnormal WBC, abnormal AG ratio, abnormal RBC, bilirubinemia, eosinophilia, hyperlipemia, increased/decreased electrolytes, increased/decreased cholesterol, increased glucocorticoids, increased LDH, increased/decreased/abnormal platelets, and increased gastrin levels. Urine abnormalities such as albuminuria, glycosuria, and hematuria were also reported. Additional isolated laboratory abnormalities were reported.

In the placebo controlled studies, when SGOT (AST) and SGPT (ALT) were evaluated, 0.4% (4/978) and 0.4% (11/2677) patients, who received placebo and PREVACID, respectively, had enzyme elevations greater than three times the upper limit of normal range at the final treatment visit. None of these patients who received PREVACID reported jaundice at any time during the study.

OVERDOSAGE
PREVACID is not removed from the circulation by hemodialysis. In one reported overdose, a patient consumed 600 mg of PREVACID with no adverse reaction.

Oral PREVACID doses up to 5000 mg/kg in rats (approximately 1300 times the 30 mg human dose based on BSA) and in mice (about 675.7 times the 30 mg human dose based on BSA) did not produce deaths or any clinical signs.



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