FDA Panel Backs Five-in-One Combination Vaccine

BY MIRIAM E. TUCKER
Senior Writer

BETHESDA, MD. — The first combination vaccine to protect against diphtheria, tetanus, pertussis, polio, and *Haemophilus influenzae* type b was deemed safe and effective by the Food and Drug Administration's Vaccines and Related Biological Products Advisory Committee vaccines advisory panel.

The panel voted unanimously to support the safety of Sanofi-Pasteur's Pentacel, which has been licensed in Canada since 1997 and used exclusively there since 1998, with over 12 million doses distributed. It also is used in several European countries.

All 15 of the panel's permanent and temporary voting members also endorsed the efficacy of the vaccine's diphtheria, tetanus, and polio components. However, a few panelists expressed concern about its protection against pertussis and Hib, based on conflicting study findings regarding noninferiority of Pentacel compared with currently licensed vaccines or their equivalents.

'Introducing this vaccine would add versatility, especially with regard to hepatitis B. If you want to give the birth dose, it simplifies the schedule.'

But even the members who voiced those concerns still generally supported the vaccine's licensure, with the caveat that ongoing disease surveillance continues and that extra efforts are made to monitor Hib rates in high-risk populations.

"For the [Hib] component, I don't feel I have adequate data," said biostatistician Steven Self, Ph.D. But, he later stated, "On balance, yes, the vaccine has public health benefit."

Indeed, several panel members noted that a small diminution in immunogenicity of one vaccine component might well be counterbalanced by improved overall vaccine coverage rates resulting from the reduction in injections.

Compared with giving DTaP, IPV, and Hib separately, use of Pentacel in children at 2, 4, 6, and 15-18 months of age would reduce the total required number of shots in infants and toddlers by seven, said Dr. David Greenberg, Sanofi-Pasteur's director of scientific and medical affairs.

Panel member Dr. John Modlin, professor of pediatrics at Dartmouth-Hitchcock Medical Center, pointed out another potential advantage to Pentacel: It would avoid the "conundrum" regarding hepatitis B vaccine, which is included in the currently licensed combination vaccines Comvax (Hib and hepatitis B) and Pediarix (diphtheria, tetanus, pertussis, hepatitis B, and polio).

Since those combinations can't be given prior to 2 months of age, infants who receive their first dose of hepatitis B vaccine at birth end up with an extra dose of hepatitis B vaccine by the time they finish the primary series. Although this is not a safety issue, it is a cost issue in some settings and has been cited as a disincentive to giving the first hepatitis B dose at birth, a practice that has been endorsed by multiple advisory bodies.

"Introducing this vaccine would add versatility, especially with regard to hepatitis B. If you want to give the birth dose, it simplifies the schedule," Dr. Modlin, former chair of the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices, said in an interview.

Sanofi-Pasteur's U.S. licensure application was based on data from five clinical studies involving a total of 7,146 Pentacel recipients. Safety and immunogenicity were examined in four studies, and one additional study examined immunogenicity compared with the company's currently licensed Daptacel (DTaP) vaccine. Two of the studies examined the concomitant use of Pentacel with Prevnar for the infant series, and with Prevnar, measles-mumps-rubella, and varicella vaccines at 15-18 months of age.

Safety data, presented by Dr. Luc Kuykens, Sanofi-Pasteur's vice president for regulatory affairs, showed no unexpected adverse events, with rates of local and systemic reactions comparable to those seen with currently licensed vaccines. Postmarketing data in Canada also support the safety of Pentacel, he said.

The FDA's safety review of Pentacel,

presented by Dr. Karen Farizo, also did not detect any unexpected problems.

However, FDA reviewer Theresa Finn, Ph.D., did identify two "concerns" with regard to Pentacel's immunogenicity, noting that the criteria for "noninferiority" were not met for the Hib and pertussis components in some of the studies.

The immunogenicity data from the five studies had been presented in detail by Dr. Michael Decker, Sanofi-Pasteur's vice president of scientific and medical affairs.

In response to Dr. Finn's analysis of the pertussis data, Dr. Decker noted that a pertussis vaccine's ability to produce immune responses to individual pertussis antigens has been shown not to correlate with degree of protection, and that Pentacel's overall protection against pertussis is comparable to currently used vaccines.

As for Hib, only one of two studies had not demonstrated noninferiority; the other one had. Moreover, the comparator in the former study was not a U.S.-licensed product, he explained.

The advisory panel was further reassured by epidemiologic data from Canada, presented by Dr. Scott Halperin, professor of pediatrics at Dalhousie University, Halifax, N.S. Multiple surveillance systems in that country confirm very low rates of pertussis and Hib disease in infants and children, he said.

In an interview following the hearing, Dr. Decker noted that only about half of U.S. physicians are using the currently available combination vaccines Comvax and Pediarix for routine infant immunization, while the other 50% are still using the separate ones. "That tells you physicians are not fully happy with their choices."

Indeed, Dr. Modlin noted, increasing competition in the combination vaccine market would be another "big advantage" of licensing Pentacel. "Competition is always a good thing, particularly with regard to public health programs." ■

Meropenem Cuts Valproic Acid Levels

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

BARCELONA — Meropenem appears to rapidly and significantly decrease serum levels of valproic acid and should be used with caution in patients who are taking the anticonvulsant, Dr. Celeste Dias reported in a poster at the annual congress of the European Society of Intensive Care Medicine.

"We strongly recommend that VPA [valproic acid] serum levels be closely monitored in these patients," said Dr. Dias of Hospital S. Joao, Oporto, Portugal.

"In high-risk patients, electroencephalographic monitoring should be considered."

We strongly recommend that valproic acid serum levels be closely monitored in these patients. In high-risk patients, EEG monitoring should be considered.

Dr. Dias presented a case review of 12 patients aged 12-78 years who were admitted to the hospital's neurological critical care unit.

Upon admission, all were taking VPA, either for a chronic seizure disorder or for prevention of seizures resulting from an acute brain disorder or injury.

During their stay in the neurological unit, all the patients began meropenem for nosocomial infections with gram-negative bacteria.

Routine serum VPA levels showed a significant and almost immediate drop in anticonvulsant levels after meropenem was initiated.

Within 60 hours, VPA levels had decreased to 20 mg/L or less in all 12 patients.

By day 6, three patients had no measurable levels of VPA during at least one blood draw.

"These decreases happened despite the fact that we actually increased VPA dosing to the maximum dose," Dr. Dias commented.

Patients were monitored with EEG and none developed acute seizures despite the drop in VPA levels.

However, Dr. Dias noted, four of the patients were also taking other anticonvulsants, including phenytoin, carbamazepine, and topiramate.

There are several possible mechanisms for this drug interaction, she said, including the inhibition of plasma protein binding and suppression of enterohepatic recirculation.

"Meropenem seems to inhibit the hydrolytic enzyme involved in the hydrolysis of VPA-glucuronide to VPA, which results in a decrease in plasma concentration of the active drug," Dr. Dias commented. ■