

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.

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 Com-

mittee 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 se-

ries, 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,

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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 dis-

ease 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. ■

*Vusion™ Ointment is indicated for the adjunctive treatment of diaper dermatitis only when complicated by documented candidiasis (microscopic evidence of pseudohyphae and/or budding yeast) in immunocompetent pediatric patients 4 weeks and older. A positive fungal culture for *C. albicans* is not adequate evidence of candidal infection since colonization with *C. albicans* can result in a positive culture. The presence of candidal infection should be established by microscopic evaluation prior to initiating treatment.

Vusion™ Ointment should be used as part of a treatment regimen that includes measures directed at the underlying diaper dermatitis, including gentle cleansing of the diaper area and frequent diaper changes.



Vusion™ Ointment should not be used as a substitute for frequent diaper changes. Vusion™ Ointment should not be used to prevent the occurrence of diaper dermatitis, since preventative use may result in the development of drug resistance.

The safety of Vusion™ Ointment when used for longer than 7 days is not known.

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BRIEF SUMMARY

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INDICATIONS AND USAGE

VUSION Ointment is indicated for the adjunctive treatment of diaper dermatitis only when complicated by documented candidiasis (microscopic evidence of pseudohyphae and/or budding yeast), in immunocompetent pediatric patients 4 weeks and older. A positive fungal culture for *Candida albicans* is not adequate evidence of candidal infection since colonization with *C. albicans* can result in a positive culture. The presence of candidal infection should be established by microscopic evaluation prior to initiating treatment.

VUSION Ointment should be used as part of a treatment regimen that includes measures directed at the underlying diaper dermatitis, including gentle cleansing of the diaper area and frequent diaper changes.

VUSION Ointment should not be used as a substitute for frequent diaper changes. VUSION Ointment should not be used to prevent the occurrence of diaper dermatitis, since preventative use may result in the development of drug resistance.

CONTRAINDICATIONS

VUSION Ointment is contraindicated in those patients with a history of sensitivity reactions to any of its components. It should be discontinued if hypersensitivity is noted.

PRECAUTIONS

General: If irritation occurs or if the disease worsens, use of the medication should be discontinued, and the health care provider should be contacted. For external use only. VUSION Ointment is for topical use only, and not for ophthalmic, oral or intravaginal use.

The safety and efficacy of VUSION Ointment has not been demonstrated in immunocompromised patients, or in infants less than 4 weeks of age (premature or term).

The safety and efficacy of VUSION Ointment have not been evaluated in incontinent adult patients. **VUSION Ointment should not be used to prevent the occurrence of diaper dermatitis, such as in an adult institutional setting, since preventative use may result in the development of drug resistance.**

Information for Patients: Patients using VUSION Ointment should receive the following information and instructions: (See Patient Package Insert)

1. VUSION Ointment is to be used only for diaper dermatitis that is complicated by documented candidiasis (i.e. documented by microscopic testing).
2. VUSION Ointment should not be used as a substitute for frequent diaper changes.
3. VUSION Ointment should not be used to prevent diaper dermatitis.
4. VUSION Ointment should not be used long term.
5. VUSION Ointment is to be used only as directed by the health care provider.
6. VUSION Ointment is for external use only. It is not to be used orally, intravaginally, or for the eyes.
7. Gently cleanse the diaper area with lukewarm water or a very mild soap and pat the area dry with a soft towel before applying VUSION Ointment.
8. Gently apply VUSION Ointment to the diaper area with the fingertips after each diaper change. Do not rub VUSION Ointment into the skin as this may cause additional irritation.
9. Thoroughly wash hands after applying VUSION Ointment.
10. Treatment should be continued for 7 days, even if there is improvement. Do not use VUSION Ointment for longer than 7 days. If symptoms have not improved by day 7, see your health care provider.
11. VUSION Ointment should not be used on children for whom it is not prescribed.

Drug Interactions: Drug-drug interaction studies were not conducted. Although women who take a warfarin anticoagulant and use a miconazole intravaginal cream or suppository may be at risk for developing an increased prothrombin time, international normalized ratio (INR) and bleeding, the potential for this interaction to occur between warfarin and VUSION Ointment is unknown.

Carcinogenesis, Mutagenesis, Impairment of fertility: Studies to evaluate the carcinogenic potential of VUSION Ointment in animals have not been performed.

Miconazole nitrate was negative in a bacterial reverse mutation test, a chromosome aberration test in mice, and micronucleus assays in mice and rats.

Miconazole nitrate had no adverse effect on fertility in a study in rats at oral doses of up to 320 mg/kg/day, which is 89 times the maximum possible topical exposure of caregivers, assuming 100% absorption.

Pregnancy Category C:

There are no adequate and well-controlled studies of VUSION Ointment in pregnant women. Miconazole nitrate administration has been shown to result in prolonged gestation and decreased numbers of live young in rats and in increased number of resorptions and decreased number of live young in rabbits at oral doses of 100 mg/kg/day and 80 mg/kg/day, which are 28 and 45 times the maximum possible topical exposure of caregivers, respectively, assuming 100% absorption.

Pregnant women should exercise appropriate precautions when administering the product.

Nursing Mothers: Safety and efficacy of the product have not been established in nursing mothers. It is not known if the active components of VUSION Ointment may be present in milk. Nursing mothers should exercise appropriate precautions when administering the product.

Pediatric Use: Efficacy was not demonstrated in infants less than 4 weeks of age. Use in infants below the age of 4 weeks is not recommended. Safety and efficacy have not been established in very-low-birth-weight infants.

VUSION Ointment should not be used to prevent diaper dermatitis.

The safety of VUSION Ointment when used for longer than 7 days is not known.

Geriatric Use: Clinical studies of VUSION Ointment did not include any subjects aged 65 and over. Safety and effectiveness in a geriatric population have not been evaluated.

ADVERSE REACTIONS

A total of 835 infants and young children were evaluated in the clinical development program. Of 418 subjects in the VUSION Ointment group, 58 (14%) reported one or more adverse events. Of 417 subjects in the zinc oxide/white petrolatum control group, 85 (20%) reported one or more adverse events. Adverse events that occurred at a rate of $\geq 1\%$ for subjects who were treated with VUSION were approximately the same in type and frequency as for subjects who were treated with zinc oxide/white petrolatum ointment.

The potential for dermal toxicity of VUSION Ointment formulation was investigated in healthy adult volunteers in four topical safety studies. These studies were conducted to assess the potential for contact phototoxicity, photoallergy, sensitization, and cumulative irritation potential. Phototesting was conducted with UV-A only. Results indicated that VUSION Ointment did not induce a contact dermal phototoxic response, contact dermal photoallergic response, or contact dermal sensitization in adult subjects. In addition, VUSION Ointment did not show any evidence of cumulative irritation potential in adult subjects.

OVERDOSAGE

VUSION Ointment is intended for topical use only. Young children are at risk for accidentally ingesting VUSION Ointment. A health care provider or poison control center should be contacted in the event of accidental ingestion.

Keep out of reach of children.

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VU-008 February, 2006
U.S. Patent No. 4,911,932

Reference: 1. Data on file, Barrier Therapeutics, Inc.

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