

## Two-Dose Vaccine May Clear FDA

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recommended following adverse events associated with the previous rotavirus vaccines, including intussusception and Kawasaki disease, and a new signal for pneumonia deaths, as well as a higher rate of convulsions in Rotarix trials.

GSK Biologicals has a postmarketing plan in place—which includes prospective clinical trials, observational studies, and “enhanced” pharmacovigilance—to collect and monitor safety data on intussusception; deaths from all causes; hospitalizations caused by pneumonia and other acute lower respiratory tract infections; convulsions; and Kawasaki disease.

If approved by the FDA, Rotarix will be the second rotavirus vaccine on the market, and the third to be approved in the United States. The first rotavirus vaccine approved, RotaShield, was withdrawn from the market after it was linked to intussusception cases. In February 2006, the FDA approved Merck & Co.’s live oral rotavirus vaccine (RotaTeq), which is administered as a three-dose series between the ages of 6 and 32 weeks.

Since 2004, Rotarix has been approved in more than 100 countries, with more than 12 million doses distributed, according to the company.

Acknowledging that “we can never prove the null hypothesis and say that the vaccine never causes intussusception,” acting panel chair John Modlin said he had a “fairly high degree of confidence with the data that I’ve seen with respect to intussusception. ... The data are very robust.” Dr. Modlin, professor of pedi-

atric at Dartmouth-Hitchcock Medical Center, Lebanon, N.H., added that it also was important to follow some of the other safety signals.

GlaxoSmithKline Inc. has proposed that Rotarix be administered in two doses, with the first dose beginning at 6 weeks and the second dose by 24 weeks of age—with an interval of at least 4 weeks between doses. In total, there have been 11 studies, mostly in Latin America, with 40,614 Rotarix and 34,739 placebo recipients receiving at least one dose. In the studies, 90%-100% of infants received both doses.

At the meeting, GSK Biologicals presented the results of two pivotal phase III efficacy trials, a study in Latin America of 17,867 infants and a European study, conducted mostly in Finland, of 3,874 infants. All the children had no obvious health problems and received the first dose at age 6 to 12-13 weeks in the Latin American study and at age 6-14 weeks in the European study.

In the Latin American study, the vaccine was 85% protective against severe rotavirus gastroenteritis and 85% protective against rotavirus gastroenteritis hospitalizations through 12 months of age—protection that was sustained through 2 years at similarly high rates, according to GSK. Efficacy against type-specific rotavirus through 24 months of age was 82% for

G1, 38% for G2, 79% for G3, 62% for G4, and 87% for G9.

In the European study, the vaccine was 87% effective against any rotavirus gastroenteritis, 96% effective against severe rotavirus gastroenteritis, 100% effective against rotavirus gastroenteritis hospitalizations, and 92% effective against medically attended rotavirus gastroenteritis; all four outcomes were sustained through two rotavirus seasons, according to the company.

It was 96% effective against type G1, 86% effective against type G2, 94% effective against type G3, 95% effective against type G4, and 85% effective against G9.

No increased risk of intussusception was associated with the vaccine in the Latin American study or in all the clinical studies.

In the Latin American study, there were six cases of intussusception within 31 days of vaccination among the Rotarix recipients vs. seven in the placebo group, a relative risk of 0.85; there was no clustering of intussusception cases within 7 or 14 days after any Rotarix dose.

In eight clinical trials, including in the United States, Latin American, Europe, and Asia, there were 27 reports of Kawasaki disease, of which 22 cases were in a large ongoing phase III study in Asia (13 cases in Rotarix recipients and 9 after placebo, for a relative risk of 1.4). But there was no temporal evidence of an association with the vaccine and Kawasaki disease in all the trials, according to GSK.

**A new signal for pneumonia deaths, as well as a higher rate of convulsions in Rotarix trials, will be monitored in postmarketing research.**

## More Pediatricians Than Family Physicians Embrace RotaTeq

BY MIRIAM E. TUCKER  
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ATLANTA — Pediatricians have embraced the current rotavirus vaccine to a much greater extent than have family physicians, Shannon Stokley said at the winter meeting of the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention.

Merck & Co.’s live, oral pentavalent vaccine RotaTeq is currently the only rotavirus vaccine available on the U.S. market. (See related story above.)

To assess the rates of adoption and attitudes toward the RotaTeq vaccine among physicians who treat children, in October 2007 the CDC sent surveys by mail and e-mail to a nationwide sample of 2,500 members of the American Academy of Pediatrics and 3,500 members of the American Academy of Family Physicians. After exclusion of those who don’t see infants under 6 months of age, the final sample of responders comprised 359 pediatricians and 264 family physicians. Responders did not differ from nonresponders with respect

to sociodemographic factors, region of the country, or practice setting or location, said Ms. Stokley of the CDC’s National Center for Immunization and Respiratory Diseases.

Pediatricians were far more likely to administer the rotavirus vaccine, with 86% versus 45% of family physicians saying they “routinely” give it. Three percent of pediatricians said they offer it but not routinely, versus 14% of family physicians, while just 11% of pediatricians do not offer the vaccine, compared with 42% of family physicians.

Similarly, 70% of pediatricians “strongly” recommend the vaccine to their patients, compared with just 22% of family physicians, while 18% and 33%, respectively, said they recommend the vaccine but not strongly. Ten percent of pediatricians versus 37% of family physicians inform patients about the rotavirus vaccine without recommending it.

Seventeen percent of pediatricians and 44% of family physicians agreed with the statement “The rotavirus vaccine is not necessary for my patients,” while 88% of pediatricians and 64% of

family physicians agreed that “Rotavirus vaccine should be routinely recommended for all eligible infants.”

Knowledge about the vaccine also differed between the two specialties. A total of 69% of pediatricians vs. 30% of family physicians knew the age by which the first dose of rotavirus vaccine should be administered (12 weeks), while 62% and 32%, respectively, knew the age by which all three doses should be administered (32 weeks).

Both specialties cited as barriers to vaccination the failure of some insurance companies to cover the vaccine (19% of pediatricians, 22% of family physicians), the “up-front” costs to purchase the vaccine (17% and 22%, respectively), and lack of adequate reimbursements (15% vs. 18%). However, concern about the safety of rotavirus vaccine was far less common among pediatricians than among family physicians (9% vs. 25%), as was concern about addition of another vaccine to the schedule (5% vs. 22%), Ms. Stokley reported.

A total of 292 of the pediatricians and 109 of the family physi-

cians said that they were familiar with a postmarketing surveillance report published on March 16, 2007, in which neither the passive Vaccine Adverse Events Reporting System nor the active Vaccine Safety Datalink identified an increased risk for intussusception following receipt of RotaTeq (MMWR 2007;56:218-22).

Of those respondents, 91% of the pediatricians versus 62% of the family physicians agreed that the number of intussusception cases reported does not exceed the number expected by chance, 8% versus 24% were uncertain about that, and 1% versus 11% said that the number of cases does exceed the number expected by chance. The report caused 3% of the pediatricians and 11% of the family physicians to stop giving the rotavirus vaccine, while it did not alter practice for 88% and 79%, respectively. Seven percent of pediatricians and 6% of family physicians said they continued to give it and told all their patients about the report.

Seventy-nine percent of pediatricians and 63% of family physicians felt that the message regarding intussusception was

In the Latin American study, there were 16 (0.05%) pneumonia deaths among vaccine recipients versus 6 (0.02%) among placebo recipients, which was not a significant difference. Nonetheless, the company plans to follow this issue after approval. In the studies, the only cause of death not balanced between placebo and vaccine recipients was pneumonia.

There also was a higher rate of convulsions over the course of the study among vaccine recipients, compared with placebo recipients (0.05% vs. 0.02%) but the rate within 31 days of vaccination was similar.

The company also presented data showing that the vaccine did not negatively affect the immune response to antigens in the Pediarix, Prevnar, and ActHiB vaccines given concurrently.

Dr. Melinda Wharton, a panel member and deputy director of the National Center for Immunization and Respiratory Diseases at the CDC, said that although there were fewer efficacy data on the G2 serotype, the overall data appeared to be robust.

She said she was not “highly concerned” about the pneumonia deaths, but added, “it is a little concerning seeing a respiratory disease signal in multiple studies.” Speculating about a possible biologic mechanism, she said that rotavirus disease in placebo recipients may be protective against respiratory infections.

Dr. Robert Davis, a panel member and director for research at the Kaiser Permanente Center for Health Research/Southeast, in Atlanta, said that assuming the increase in pneumonia deaths is real, the risk would be “compensated many times over by a decrease in deaths due to natural rotavirus disease,” although there were no data to show this effect. ■

communicated clearly, while about a third of each group felt that the findings should not have been publicized because they raised concern unnecessarily.

In the discussion that followed Ms. Stokley’s presentation, AAFP coliaison Dr. Jonathan Temte of the University of Wisconsin, Madison, said that family physicians “have a long tradition of a little bit of skepticism” about recommendations because of their broad scope of practice and that, moreover, he has noticed a certain degree of “vaccine fatigue” among family physicians because of the rapid increase in new vaccines and new recommendations over the last few years. “I think that has to be kept in mind so we don’t lose what has been a very strong ally over the last few years for immunization practice,” Dr. Temte added.

Dr. Doug Campos-Outcalt, the other AAFP coliaison, said that the lack of adequate reimbursement for vaccine administration is a major issue among family physicians. “They lose money on each vaccine ... to the point of diminishing returns. I think we’ve got to address this issue.” ■