

Food and Drug Administration Approval for Use of Hiberix as a 3-Dose Primary *Haemophilus influenzae* Type b (Hib) Vaccination Series

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On January 14, 2016, GlaxoSmithKline Biologicals (Research Triangle Park, North Carolina) received approval from the Food and Drug Administration (FDA) to expand use of Hiberix (Haemophilus b Conjugate Vaccine [Tetanus Toxoid Conjugate]) for a 3-dose infant primary vaccination series at ages 2, 4, and 6 months. Hiberix was first licensed in the United States in August 2009 for use as a booster dose in children aged 15 months through 4 years under the Accelerated Approval Regulations, in response to a *Haemophilus influenzae* type b (Hib) vaccine shortage that lasted from December 2007 to July 2009 (1). Expanding the age indication to include infants provides another vaccine option in addition to other currently licensed monovalent or combination Hib vaccines recommended for the primary vaccination series.* Hiberix contains 10 μ g purified capsular polyribosyl ribitolphosphate (PRP) conjugated to 25 μ g tetanus toxoid (PRP-T) and is supplied as a single-dose vial of lyophilized vaccine to be reconstituted with saline diluent. For the 3-dose primary series, a single (0.5 mL) dose should be given by intramuscular injection at ages 2, 4, and 6 months; the first dose may be given as early as age 6 weeks. The recommended catch-up schedule for PRP-T vaccines (<http://www.cdc.gov/vaccines/schedules/hcp/child-adolescent.html>) should be followed. As previously recommended, a single booster dose should be administered to children aged 15 months through 18 months; to facilitate timely booster vaccination, Hiberix can be administered as early as age 12 months, in accordance with Hib vaccination schedules for routine and catch-up immunization (1–3).

Immunogenicity and Safety

Immunogenicity and safety data for the use of Hiberix as a primary vaccination series in infants are from a phase three,

single-blind, randomized, multicenter study conducted among 4,003 healthy infants treated at 67 sites in the United States (4). Noninferiority of Hiberix to ActHIB (U.S.-licensed monovalent Haemophilus b Conjugate Vaccine [Tetanus Toxoid Conjugate], manufactured by Sanofi Pasteur, Swiftwater, PA) was assessed 1 month after completion of the primary series (after dose 3) using anti-PRP antibody concentrations $\geq 0.15\mu\text{g/mL}$ and $\geq 1.0\mu\text{g/mL}$. Based on animal and human studies, anti-PRP levels of $\geq 0.15\mu\text{g/mL}$ and $\geq 1.0\mu\text{g/mL}$ provide protection from invasive Hib disease in the short- and long-term, respectively.

For each study group, Hiberix was coadministered with recommended routine childhood vaccines (Pediarix [diphtheria and tetanus toxoids and acellular pertussis (DTaP)/hepatitis B (HepB)/inactivated poliovirus (IPV)]; Prevnar13 [Pneumococcal 13-valent Conjugate Vaccine], and Rotarix [Rotavirus Vaccine, Live, Oral Suspension]), and noninferiority of immune responses to antigens contained in the coadministered vaccines, with the exception of Rotarix, was assessed. Adverse events with onset <31 days after each vaccination were recorded and physician-verified serious adverse events were reported from time of vaccination through 6 months after vaccination.

Immunogenicity. Approximately 2,000 infants were included in the immunogenicity assessment. One month after dose 3, anti-PRP concentrations $\geq 0.15\mu\text{g/ml}$ and $\geq 1.0\mu\text{g/ml}$ were achieved in 96.6% and 81.2% of infants who received Hiberix, respectively, and in 96.7% and 89.8% of infants who received ActHIB, respectively. Noninferiority criteria were met for anti-PRP response $\geq 0.15\mu\text{g/ml}$, but were not met for anti-PRP response $\geq 1.0\text{ g/ml}$. Noninferiority criteria were met for the following antigens contained in coadministered vaccines: 13 serotypes of *Streptococcus pneumoniae*; poliovirus types 1, 2, and 3; hepatitis B; pertussis toxin, filamentous hemagglutinin, and pertactin; diphtheria; and tetanus.

An open label study compared Pentacel (DTaP/IPV/Hib combination vaccine) and Hiberix at 1 month after dose 3; noninferiority was not assessed as a primary objective. The percentages of infants with titers $\geq 0.15\mu\text{g/ml}$ and $\geq 1.0\mu\text{g/ml}$ were higher after the 3rd dose of Hiberix (96.6% and 81.2%, respectively) than after the 3rd dose of Pentacel (92.5% and 78.3%, respectively).

*PedvaxHib (Haemophilus b Conjugate Vaccine [Meningococcal Protein Conjugate] manufactured by Merck & Co., Kenilworth, NJ) (<http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm253644.htm>); ActHIB (Haemophilus b Conjugate Vaccine [Tetanus Toxoid Conjugate], manufactured by Sanofi Pasteur, Swiftwater, PA) (<http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm094028.htm>); Pentacel (Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate [Tetanus Toxoid Conjugate] Vaccine, manufactured by Sanofi Pasteur) (<http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm094030.htm>); and MenHibrix (Meningococcal Groups C and Y and Haemophilus b Tetanus Toxoid Conjugate Vaccine, manufactured by GlaxoSmithKline Biologicals, Research Triangle Park, NC) (<http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm308566.htm>).

Safety. Approximately 3,500 vaccinated infants were included in the safety assessment. Injection site pain, irritability, and drowsiness were the most frequently reported adverse events; rates were similar for Hiberix, ActHIB, and Pentacel. Fever >103.1°F (39.5°C) occurred in <1% of infants in all study groups. No deaths occurred. Nonfatal serious adverse events were reported for 3.6%, 4.6%, and 4.0% of infants receiving Hiberix, ActHIB, and Pentacel, respectively; one serious adverse event in the Hiberix group was considered related to vaccine administration (afebrile seizure 14 days after dose 1; the patient had no apparent seizure disorder at 1 month after dose 3).

Further information is available in the package insert (<http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM179530.pdf>).

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References

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