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 10μg purified capsular polyribosyl ribitolphosphate (PRP) conjugated to 25μg 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 ≥0.15μg/mL and ≥1.0μg/mL. Based on animal and human studies, anti-PRP levels of ≥0.15μg/mL and ≥1.0μg/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 ≥0.15μg/ml and ≥1.0μg/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 ≥0.15μg/ml, but were not met for anti-PRP response ≥1.0 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 ≥0.15μg/ml and ≥1.0μg/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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