

Pharmacovigilance Plan Review - March 27, 2009 - Hiberix

PHARMACOVIGILANCE PLAN REVIEW OBE/DE

Date: March 27, 2009

FDA STN: 125347

Sponsor: GlaxoSmithKline

Product: Haemophilus B Conjugate Vaccine (Tetanus Toxoid Conjugate)
[Proposed proprietary name: Hiberix]

Indication: Active immunization as a booster dose for the prevention of invasive disease caused by *Haemophilus influenzae* type b (Hib) in children 15 months through 4 years of age (prior to 5th birthday).

To: BLA Review Committee

From: David Menschik, MD, MPH
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Through: Andrea Sutherland, MD, MSc, MPH
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In the Biologic License Application (BLA) referenced above, the sponsor is seeking initial approval in the United States for its *Haemophilus B* Conjugate Vaccine (Tetanus Toxoid Conjugate), Hiberix (proposed trade name). Hiberix is currently licensed in 98 countries (first licensed in Germany in June, 1996) and over -b(4)-million doses have been distributed worldwide. This BLA seeks licensure for active immunization as a booster dose for the prevention of invasive disease caused by *Haemophilus influenzae* type b (Hib) in children 15 months through 4 years of age (prior to 5th birthday). This BLA is being reviewed according to an accelerated priority review process in the context of a nationwide shortage of Hib vaccine.

In the application the sponsor presents safety data from seven clinical studies in which Hiberix was used as a booster dose (at age 11-25 months; total sample size ~1,000), and from two supportive clinical studies in which Hiberix was administered as part of a primary vaccination series (at 2, 4, and 6 months; total sample size ~1,400). In accordance with the priority review process, the sponsor has committed to performing a confirmatory postmarketing study. The proposed confirmatory study would evaluate safety in an additional ~1650 Hiberix booster recipients 15-18 months of age. Safety for this vaccine as a catch-up booster vaccination (i.e., administered after the Advisory Committee on Immunization Practices recommended age) is being extrapolated upwards in age through 4 years (prior to 5th birthday). Discussion of a potential larger scale postmarketing safety study is being deferred pending the results of the postmarketing confirmatory study. The sponsor has identified three categories of adverse events warranting enhanced postmarketing surveillance with expedited reporting: deaths, leukocytoclastic vasculitis, and type III (immune complex-mediated) hypersensitivity reactions. The pharmacovigilance plan is generally adequate although the sponsor should provide additional details of enhanced pharmacovigilance procedures for evaluating specified adverse events.

Recommended comments for the sponsor:

1. Please specify your enhanced pharmacovigilance procedures for evaluating the three identified adverse events (deaths, leukocytoclastic vasculitis, and type III hypersensitivity reactions), as well as potential unanticipated safety signals.
2. We recommend that the following post-marketing adverse events should also be reported in an expedited fashion in addition to 21 CFR 600.80 requirements. This expanded adverse experience reporting should be provided as 15-day reports to the Vaccine Adverse Event Reporting System for one year following product licensure as follows:
All serious adverse events whether expected/labeled or unexpected/unlabeled, including but not limited to vaccine failure, seizures, shock, respiratory distress or difficulty breathing, angioedema, inspiratory stridor, and bilateral wheezing.
3. We acknowledge that we are deferring discussion of a potential larger scale postmarketing safety study pending the results of your postmarketing confirmatory study (Hib-097).
4. Please acknowledge that post-licensure distribution reports will be submitted to CBER on a monthly basis for one year following licensure and then at least every six months in accordance with 21 CFR 600.81.

