Pharmacovigilance Plan - 12/12/2007 - KINRIX

Date: December 12, 2007
From: Soju Chang, MD, MPH
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To: Michael J. Schmitt, PhD
Chair, KinrixT Biologics License Application Review Committee
Through: Robert Ball, MD, MPH, ScM
Chief, Vaccine Safety Branch
Re: Pharmacovigilance Plan for STN 125260/0 [Biologics License Application for Diphtheria and Tetanus Toxoids, Acellular Pertussis and Inactivated Poliovirus Combined Vaccine as a Booster Dose to Children 4-6 years of Age]

Introduction

On April 06, 2007, GlaxoSmithKline (GSK) Biologicals submitted a Biologics License Application for Diphtheria and Tetanus Toxoids, Acellular Pertussis and Inactivated Poliovirus (DTaP-IPV) vaccine [trade name KinrixT]. The DTaP-IPV candidate vaccine consists of a combination of GSK's Diphtheria and Tetanus Toxoids and Acellular Pertussis (DTaP) vaccine (Infanrix®; STN 103647, approved January 29, 1997) and inactivated poliovirus vaccine (IPV). The IPV component is not licensed as a stand-alone IPV vaccine in US. The DTaP and IPV components are the same as those found in GSK's Pediarix® [Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine Combined; STN 103907; approved December 13, 2002]. All components of the vaccine have been previously studied and licensed for use. DTaP-IPV will be indicated for active immunization against diphtheria, tetanus, pertussis and poliomyelitis, administered as the 5th dose of DTaP and as the 4th dose of IPV in children 4-6 years of age.

GSK Biologicals markets a combined diphtheria, tetanus, acellular pertussis and inactivated poliovirus vaccine, currently approved in 31 countries outside of the US and marketed under the names Infanrix-Polio, Infanrix-IPV, and Infanrix tetra. The vaccine is indicated for primary immunization from the age of 2 months against diphtheria, tetanus, pertussis and poliomyelitis and as a booster dose for children who have previously been immunized with DTP and polio antigens. The formulation is identical to that of the US candidate vaccine, with the exception that the vaccine distributed outside of the US contains ≤2.5µg 2-phenoxyethanol per dose. The total patient exposure can be calculated from the number of doses distributed. From the first launch in August 1996 until 06 August 2006, ---------- doses were distributed. The primary vaccination schedule consists of three doses in the first year of life and can start from the age of 2 months. Therefore, it can be estimated that the number of patients exposed is between ---------- individuals, assuming all doses distributed were administered.

Safety Specification

Important Identified Risks/ Important Potential Risks/Important Missing Information

GSK Biologicals considers adverse events (AEs) of large local swelling reactions and stroke as safety aspects of interest. At this stage, based on available data, both from

clinical development and from post-marketing surveillance, the company does not consider the above mentioned AEs to be potential risks associated with the candidate DTaP-IPV vaccine. Nevertheless, in further compliance with the applicable guidance, GSK Biologicals will continue to monitor these safety aspects.

Non-clinical

No non-clinical studies were conducted in support of this application. The antigens included in the candidate DTaP-IPV vaccine are well-characterized and have been used for many years as components of other US-licensed vaccines.

Clinical

Limitations of the human safety database

Three pre-licensure clinical studies involved a total of 3,537 children 4 to 6 years of age vaccinated with DTaP-IPV: one pivotal, lot-to-lot consistency study (n=3,156) and one supportive study (n=200) in US; one supportive study (n=181) in Australia. In these clinical trials, safety was evaluated among DTaP-IPV recipients as compared to those who received separate, concomitant administration of Infanrix® and Sanofi pasteur's IPOL® (DTaP+IPV). All subjects received concomitant measles mumps and rubella (MMR) vaccine. Solicited local (e.g., pain, redness, swelling including extensive limb swelling) and systemic (fever, drowsiness, loss of appetite) AEs as well as unsolicited AEs were evaluated.

Populations not studied in the pre-approval phase

The candidate vaccine has not been studied in immunosuppressed individuals or those with chronic diseases during the pre-authorization phase. According to current Advisory Committee on Immunization Practices (ACIP) recommendations, vaccines that include only *inactivated* virus, such as DTaP-IPV, may be safely used in these circumstances; however, the effectiveness might be suboptimal. The use of the candidate vaccine has not been studied in children whose age is outside of the intended age range for the vaccine (i.e., children younger than 4 or older than 6 years of age).

Adverse events (AEs)/adverse drug reactions (ADRs)

Regarding solicited local AEs, in the pivotal study, based on two-sided Fisher's exact test, differences between the pooled DTaP-IPV and DTaP+IPV control groups were noted as follows: 1) The percentage of subjects reporting Grade 3 pain at any injection site was greater in the pooled DTaP-IPV group than in the DTaP + IPV control group (1.6% vs 0.7%; $p<0.05$); 2) The percentages of subjects reporting any or Grade 3 pain at the DTaP-based injection site, was greater in the pooled DTaP-IPV groups (57.0% and 1.6%, respectively) than in the DTaP + IPV control group (53.3% and 0.6%, respectively; $p<0.05$ for both comparisons); 3) The percentage of subjects reporting redness ≥110mm diameter at any injection site, or any redness at the MMRII injection site, was greater in the DTaP + IPV control group (4.2% and 9.6%, respectively) than in the DTaP-IPV group (2.9% and 7.2%, respectively; $p<0.05$ for both comparisons). There were no statistically significant differences between the DTaP-IPV pooled group and the control group in terms of the percentages of subjects who sought medical advice for any local solicited AE.

In the US supportive study, no significant differences ($p <0.05$) were observed between groups in the incidence or intensity of solicited local symptoms. Large injection site swelling reactions were defined for both studies as any local swelling with diameter greater than 50mm, any increase in mid upper arm circumference greater than 30mm,

or any diffuse swelling preventing or interfering with everyday activities such as writing, drawing, playing, eating, school or daycare attendance, or sleeping. The proportions of subjects reporting large injection site swelling reactions were similar between the pooled DTaP-IPV groups and the DTaP + IPV group in the pivotal study. No comparative statement was made for US supportive study. The Australian supportive study showed that a similar incidence of large swelling reactions was observed after DTaP-IPV or DTaP+IPV booster vaccination. There was no difference between the two groups in incidence and intensity of solicited symptoms occurring after vaccination.

For both US studies, the proportions of subjects reporting solicited general AEs was generally comparable between the pooled DTaP-IPV group and DTaP + IPV control group. There was a significantly greater percentage of subjects reporting fever >38°C in the DTaP-IPV group than in the DTaP + IPV control group. Because there were no statistically significant differences in the proportions of subjects with fever >38.5°C or in the proportion of subjects seeking medical advice for fever or any other solicited general AEs, the difference at the lower temperature range was not considered clinically relevant. There were no apparent differences between groups in the reporting of MMR-specific general symptoms.

No clinically relevant differences between treatment and control groups were detected with regard to reporting of specific unsolicited AEs in either US study. There were no deaths reported. None of serious AEs (e.g., hypernatremia and dehydration, gastroenteritis and dehydration, asthma, pneumonia) were considered by the investigators to be related to study vaccination. In the US pivotal study, 12 serious AEs (4 with unresolved and 8 with resolved outcomes) in the DTaP-IPV group (n=3,156) and 4 serious (all with resolved outcomes) in the DTaP + IPV control group (n=1,053) were reported during the entire study period. The four serious AEs with unresolved outcomes included: a 4-year old female with family history of thrombotic events developed cerebrovascular accident (CVA) 30 days after vaccination; a 4-year old male developed necrotizing pneumonia 172 days after vaccination; a 4-year old male developed optic atrophy 180 days after vaccination; and a 5-year old male developed Burkitt's lymphoma 155 days after vaccination. In the US supportive study, 3 serious AEs (all with resolved outcomes) in the DTaP-IPV group (n=200) and 2 serious (all with resolved outcomes) in the DTaP + IPV control group (n=200) were reported during the entire study period. In the Australian supportive study, no serious AEs were reported following the booster dose of DTaP-IPV (n=181).

In response to CBER's request following review of GSK's pre-BLA meeting briefing document, the company prepared a Biologicals Clinical Safety and Pharmacovigilance summary of events medically consistent with stroke, hypercoagulable states, or thrombotic events collected through postmarketing pharmacovigilance activities for DTaP-IPV, *Infanrix*, and *Pediarix* vaccines. Cases were initially identified by searching GSK's worldwide clinical safety database for MedDRA Preferred Terms likely to be associated with CVA, thrombosis or hypercoagulable states. This was followed by medical review of case summaries associated with these terms for selection of cases whose clinical features were consistent with the diagnostic criteria for stroke, thrombosis, thromboembolism, or hypercoagulable states. Finally, cases consistent with the diagnostic criteria for these events were assessed for possible relationship to vaccination with DTaP-IPV, *Infanrix*, or *Pediarix*, considering the following criteria: the

time to onset of the event relative to vaccination and possible causes other than vaccination such as an alternative diagnosis, concurrent disease, or concurrent drug. The analysis included all events reported to GSK as of 1 January 2007. It was concluded that the available data do not support an association between vaccination with the candidate DTaP-IPV, *Pediarix*, or *Infanrix* and cerebrovascular accident, thrombosis, thromboembolism, or hypercoagulable states.

Identified and potential interactions, including food-drug and drug-drug interactions

Co-administration of DTaP-IPV vaccine with other vaccines has not been studied with the exception of MMR vaccine. Co-administration of MMR with DTaP-IPV, compared to co-administration with DTaP + IPV, did not produce any clinically-important differences in the safety profiles of either vaccine. As previously discussed with the agency, post-marketing studies will include evaluation of co-administration of the DTaP-IPV candidate vaccine with varicella vaccine. In patients receiving immunosuppressive therapy or patients with immunodeficiency an adequate immunologic response may not be achieved.

Epidemiology

In USA, the incidences of these vaccine-preventable diseases (polio, diphtheria, tetanus and pertussis) have dramatically declined in the past few decades, in particular among children under 5 years of age. Regarding the epidemiology of potential safety risks, a study shows that entire proximal limb swelling occurs in 2% to 6% of children given booster doses of DTaP vaccines. The annual incidence of stroke in US children less than 15 years of age is between 2.3 and 6.4 (95% CI: 2.5, 10.4) per 100,000.

Pharmacological class effects

Large local injection site reactions have been documented with successive doses of DTaP vaccines with the highest rates reported after the 4th and 5th consecutive doses. Skowronski [2003] evaluated several clinical studies and reported that entire proximal limb swelling occurs in 2% to 6% of children given booster doses of DTaP vaccines. Rennels [2000] and Rennels [2003] reported that swelling reactions generally lasted a few days and resolved without sequelae.

Summary

The company concludes that currently available safety and efficacy data from the clinical trials conducted with candidate DTaP-IPV vaccine do not indicate any safety risks. Analyses of the available data have identified two safety aspects of interest: large injection site swelling reactions, and, from a single clinical trials case, stroke. Large injection site swelling reactions have been classified as a safety aspect of interest based on the association between pertussis-containing vaccines, in general, and large local reactions. The information that can be defined according to applicable guidance as missing or incomplete at this stage in the life-cycle of the candidate DTaP-IPV vaccine relates to the populations not thoroughly investigated in the pre-authorization phase - immunocompromised children, and children with chronic diseases. However, according to current recommendations, the candidate vaccine may be safely used in these circumstances.

Action Plan for Safety Issues/ Summary of Actions to Be Completed, Including Milestones

To establish enhanced passive surveillance consisting of closely monitoring all worldwide spontaneously reported large injections site swelling reactions and stroke,

thrombus, thromboembolisms, hypercoagulable states. The objective is to obtain as much follow-up information as possible. Efforts will include use of a questionnaire to obtain a standardized and detailed description of the cases. All spontaneous reports of CVA and related events will be expedited to the Agency. Additional milestones for evaluation and reporting will be agreed upon with the Agency.

Comments

- Please revise the proposed action plan for Stroke, Hypercoagulable state, Thrombus, Thromboembolism [page 23 in "DTaP-IPV United States Risk Management Plan June 2007"]. The plan stated "GSK Biologicals is closely monitoring all worldwide spontaneously reported large injections site swelling reactions." instead of "GSK Biologicals is closely monitoring all worldwide spontaneously reported stroke, hypercoagulable state, thrombus, thromboembolism events.".
- Please submit reports of CVA and related events and large injections site swelling reaction as 15-day reports.
- "Drug administration error" was listed as one of the top 10 most frequently reported AEs for DTaP-IPV vaccine in the post-marketing setting. Please evaluate the AE drug administration error and provide an action plan as appropriate according to the March 2005 document entitled "International Conference on Harmonisation (ICH); Guidance for Industry: E2E Pharmacovigilance Planning".
- Please include, in the proposed DTaP-IPV pharmacovigilance plan, monitoring of AEs with known (i.e., evidence favors a causal relation) or potential (i.e., evidence is inadequate to accept or reject a causal relation) association with one or more DTaP-IPV vaccine components as determined by the Immunization Safety Review Committee of Institute of Medicine or National Vaccine Injury Compensation Program. Examples include diphtheria and tetanus toxoids and anaphylaxis, tetanus toxoid and brachial neuritis, pertussis and encephalopathy, tetanus toxoid and demyelinating diseases of central nervous system such as optic neuritis.
- Please evaluate febrile seizure as a potential safety concern for the candidate vaccine DTaP-IPV and provide an action plan as appropriate according to the March 2005 document entitled "International Conference on Harmonisation (ICH); Guidance for Industry: E2E Pharmacovigilance Planning". As described in the proposed DTaP-IPV pharmacovigilance plan, there was a significantly greater percentage of subjects reporting fever >38°C in the DTaP-IPV group than in the DTaP + IPV control group in the pivotal study. Febrile seizures occur in children with a body temperature above 38°C and most often in young children (e.g., children aged 9 to 20 months), but it can occur in children aged 3 months through 6 years.
- Please note that the number of doses distributed worldwide for GSK's combined diphtheria, tetanus, acellular pertussis and inactivated poliovirus vaccine (approximately ---------- doses) seems like a small number of doses distributed for a vaccine that has been licensed for over 10 years and in 31 countries.