

STN 125563

Toxicology Review of PR5I (Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus, Haemophilus b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B [Recombinant] Vaccine)

BLA: 125563

Sponsor: Sanofi Pasteur Inc. and Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc.

Reviewer: Steven Kunder, Ph.D., DABT

Division: OVRD/DVRPA

Proposed use: PR5I is indicated for active immunization against diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, and invasive disease due to *H. influenzae* type b. PR5I is proposed for use as a 3 dose series in children from 6 weeks through 4 years of age (up to the 5th birthday).

TOXICOLOGY STUDY:

AR5I and PR5I (b) (4) Vaccines -Extended Single Dose Toxicity Study by the Intramuscular Route in the Rat" (Study no. 407/121)

The above toxicology study was reviewed under IND 14496 by Nabil Al-Humadi, Ph.D.

No other toxicology studies (repeat dose toxicology, reproductive and developmental toxicology, genotoxicity or carcinogenicity) were conducted for the nonclinical support of this product.

TABLE OF CONTENTS

<u>1</u>	<u>INTRODUCTION</u>	<u>3</u>
<u>3</u>	<u>CONCLUSION</u>	<u>3</u>
<u>4</u>	<u>PROPOSED PACKAGE INSERT WORDING</u>	<u>4</u>
<u>5</u>	<u>OVERALL CONCLUSION</u>	<u>4</u>

INTRODUCTION

PR5I vaccine is a hexavalent pediatric combination vaccine containing Diphtheria (D) and Tetanus (T) toxoids, acellular Pertussis (5-component; aP), Inactivated Poliomyelitis virus (IPV), Hepatitis B (HepB) surface antigen and *Haemophilus influenza* type b (Hib) polysaccharide conjugated to meningococcal outer membrane protein complex (OMPC) and is adjuvanted with amorphous aluminum hydroxyphosphate sulfate and aluminum phosphate. All PR5I antigens are components of combination and monovalent vaccines currently licensed in the US. PR5I contains the same DTaP as Pentacel in combination with IPV (from Vero cells), which is in IPOL, OMPC-conjugated polyribosylribitol phosphate (PRP; a Hib antigen), which is in PedvaxHIB, and recombinant hepatitis B surface antigen (HBsAg), which is in Recombivax HB. In addition, several vaccines containing one or more of the antigens in PR5I have been licensed in the US, EU, and/or other countries, including a hexavalent vaccine (Hexaxim/Hexyon/Hexacima), two pentavalent vaccines (Pentacel and Pentavac/Pentaxim) and two tetravalent vaccines (Adacel/Covaxis and Tetravac/Tetraxim), each containing similar D, T, and IPV and two or more of the same pertussis antigens, as well as HBVAXPRO (HepB antigen alone).

The safety and immunogenicity of 4 investigational hexavalent vaccine formulations was evaluated in Phase I and II studies in infants and toddlers. In Phases I and IIa, the 4 formulations were identical in composition but differed in the dose (b) (4)

For Phases IIb and III, an optimal formulation, PR5I (3 µg PRP-OMPC per vaccine dose and 10 µg HBsAg per vaccine dose), was selected based on favorable safety and tolerability data as well as acceptable immunogenicity data that were obtained from previous clinical studies.

The nonclinical toxicology evaluation of PR5I was intended to confirm the safety profile of the combination of the individual antigens in PR5I in a single dose study in rats. This study supported both the Phase I study and the subsequent clinical trial program.

PR5I is indicated for active immunization against diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, and invasive disease due to *H. influenzae* type b. PR5I is proposed for use as a 3 dose series in children from 6 weeks through 4 years of age (up to the 5th birthday).

The three-dose immunization series consists of a 0.5 mL intramuscular injection, administered at 2, 4, and 6 months of age.

CONCLUSION

To support PR5I development, a single dose toxicology study was conducted in rats to confirm the safety profile of D, T, aP, IPV, Hib, and Hep B antigens when combined together in PR5I. This study showed that IM injection of PR5I was well tolerated. Some minor changes were observed which were transient including: transient effects on female body weight and slightly higher neutrophil levels associated with slightly lower lymphocyte count, when compared to concurrent controls. These changes were all reversible within 2 weeks. At the injection sites, an inflammatory reaction was observed by histological examination. Following recovery after 14 days, local changes at the injection site persisted including granuloma in the muscle, superficial granuloma, plasma cell infiltration, and muscle cell degeneration. These findings are typical of immunologically active vaccines and may reflect both the intended immune response

and secondary injection site tissue damage. Inflammatory and repair mechanisms are demonstrated by the histologic findings at the injection site.

No safety issues were demonstrated by this toxicology study. This submission is acceptable with respect to nonclinical toxicology.

PROPOSED PACKAGE INSERT WORDING

8.1 Pregnancy

Pregnancy Category C

"Animal reproduction studies have not been conducted with (b) (4) . It is also not known whether (b) (4) can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. (b) (4) is not recommended for use in women of childbearing age."

The sponsor characterization of pregnancy category for the product is accurate.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

"(b) (4) has not been evaluated for carcinogenic or mutagenic potential or impairment of fertility."

The sponsor characterization of carcinogenesis, mutagenicity and impairment of fertility for the product is accurate.

OVERALL CONCLUSION

Based on nonclinical toxicity assessments, there are no significant safety issues to preclude the BLA from being approved.

Concurrence: Martin D. Green