



**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology
Division of Epidemiology**

ADDENDUM: PERIODIC BENEFIT-RISK EVALUATION REPORT REVIEW

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[Please note that the Branch Chief has signed on behalf of Dr. Rohan.]

Subject: Periodic Safety Update Reports (PSURs)
Update on any late-breaking safety information
US Package Insert, Section 6.2 proposed labeling

Applicant: MCM Vaccine Company

Product: PR5I
VAXELIS® (proposed trade name)
Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine
Adsorbed, Inactivated Poliovirus, Haemophilus b Conjugate
[Meningococcal Protein Conjugate] and Hepatitis B
[Recombinant] Vaccine (DTaP-IPV-Hib-HepB)

Purpose of Submission: To provide postmarketing safety experience outside the US

STN: BLA 125563/4.0

Complete Response Resubmission Date: June 29, 2018

PBRER Submission Date: October 19, 2018

Action Due Date: December 29, 2018

1. Introduction

1.1. Objectives

The purpose of this review is to identify potential safety issues from review of data from the most recent PSURs and from the update of any late-breaking safety issues for VAXELIS that would impact the current pharmacovigilance plan (PVP) in advance of approval.

1.2. Background

The original BLA, 125563.0, was submitted to CBER on August 12, 2014, with the proposed trade name “(b) (4)”. A Major Amendment was submitted on July 6, 2015. OBE/DE completed a review of the relevant safety-related information, found no significant safety issues, and concurred with the applicant’s proposal to conduct routine pharmacovigilance. The corresponding OBE/DE review memo was uploaded to the EDR on March 10, 2015. No new PVP has been submitted and the Periodic Safety Update Reports (PSURs) are reviewed to ensure that there are no new safety issues identified since licensure outside the US.

CBER issued a Complete Response (CR) on November 1, 2015, due to manufacturing and product issues. The applicant’s Response to CR, submitted as amendment 125563/0.36, on June 29, 2018, has satisfactorily resolved all CR issues.

The product was approved in the European Union via Centralized Procedure on February 15, 2016, with the Trade Name, VAXELIS and is currently approved in 31 countries. Therefore, CBER requested the most recent Periodic Safety Update Report (PSUR) containing VAXELIS worldwide postmarketing experience and the report was submitted as supplement 125563/4.0 on October 19, 2018.

VAXELIS is a vaccine for active immunization to prevent diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, and invasive disease due to Haemophilus influenzae type b. VAXELIS is proposed to be licensed as a 3-dose series in children from 6 weeks through 4 years of age (prior to the 5th birthday). The 3-dose immunization series consists of a 0.5 mL intramuscular injection, administered at 2, 4, and 6 months of age.

2. REVIEW MATERIALS

VAXELIS Periodic Safety Update Reports (PSUR) covering the period from initial licensure in the EU, February 15, 2016, to August 15, 2018.

Summary describing any late-breaking safety issues for the period from August 16, 2018, through November 27, 2018.

VAXELIS draft US Package Insert (USPI).

3. REVIEW OF POSTMARKETING SAFETY UPDATE REPORTS (PSURS)

VAXELIS is approved in 31 countries and no registration has been revoked or withdrawn for safety reasons.

An estimated (b) (4) doses have been distributed worldwide since market introduction on February 15, 2016. Approximately 319,518 to (b) (4) individuals have received VAXELIS based upon the assumption that each individual received 1 to 4 doses and that all distributed doses were administered.

There have been no regulatory or manufacturer actions related to VAXELIS® (DTaP-HB-IPV-Hib) due to safety reasons, and no safety related updates were made to either the Investigator's Brochure or the Company Core Safety Information.

3.1. First PSUR (February 15, 2016, through August 15, 2016)

3.1.1. Important Identified Risks

None

3.1.2. Important Potential Risks

- Hypersensitivity including Anaphylactic reactions
- Convulsions including febrile convulsions
- Hypotonic-Hyporesponsive Episodes
- Encephalopathy/Encephalitis
- Apnoea (in premature infants less than or equal to 28 weeks gestation)
- Extensive Limb Swelling

3.1.3. Missing Information

- Infants less than 6 weeks of age
- Premature infants less than 28 weeks of gestation at the time of birth
- Immunocompromised patients
- Use in children > 15 months of age
- Duration of protection with pertussis antigens

3.1.4. Signal Evaluation

No signal evaluations were ongoing or completed during the PSUR reporting interval.

3.1.5. New clinical study and postmarketing data

None

3.2. Second PSUR (August 16, 2016 to February 15, 2017)

3.2.1. Important Identified Risks

None

3.2.2. Important Potential Risks

- Hypersensitivity including Anaphylactic reactions
- Convulsions including febrile convulsions
- Hypotonic-Hyporesponsive Episodes
- Encephalopathy/Encephalitis
- Apnoea (in premature infants less than or equal to 28 weeks gestation)
- Extensive Limb Swelling

3.2.3. Missing Information

- Infants less than 6 weeks of age
- Premature infants less than 28 weeks of gestation at the time of birth
- Immunocompromised patients
- Use in children > 15 months of age
- Duration of protection with pertussis antigens

3.2.4. Signal Evaluation

No signal evaluations were ongoing or completed during the PSUR reporting interval.

3.2.5. New clinical study and postmarketing data

None

3.3. Third PSUR (February 16, 2017 – August 15, 2017)

3.3.1. Important Identified Risks

None

3.3.2. Important Potential Risks

- Hypersensitivity including Anaphylactic reactions
- Convulsions including febrile convulsions
- Hypotonic-Hyporesponsive Episodes
- Encephalopathy/Encephalitis
- Apnoea (in premature infants less than or equal to 28 weeks gestation)
- Extensive Limb Swelling

3.3.3. Missing Information

- Infants less than 6 weeks of age
- Premature infants less than 28 weeks of gestation at the time of birth
- Immunocompromised patients
- Use in children > 15 months of age
- Duration of protection with pertussis antigens

3.3.4. Signal Evaluation

No signal evaluations were ongoing or completed during the PSUR reporting interval.

3.3.5. New clinical study and postmarketing data

None

3.4. Fourth PSUR (August 16, 2017 – February 15, 2018)

3.4.1. Important Identified Risks

None

3.4.2. Important Potential Risks

- Hypersensitivity including Anaphylactic reactions
- Convulsions including febrile convulsions

- Hypotonic-Hyporesponsive Episodes
- Encephalopathy/Encephalitis
- Apnoea (in premature infants less than or equal to 28 weeks gestation)
- Extensive Limb Swelling

3.4.3. Missing Information

- Infants less than 6 weeks of age
- Premature infants less than 28 weeks of gestation at the time of birth
- Immunocompromised patients
- Use in children > 15 months of age
- Duration of protection with pertussis antigens

3.4.4. Signal Evaluation

No signal evaluations were ongoing or completed during the PSUR reporting interval.

3.4.5. New clinical study and postmarketing data

None

3.5. Fifth PSUR covering the period from February 16, 2018 to August 15, 2018

3.5.1. Important Identified Risks

None

3.5.2. Important Potential Risks

- Hypersensitivity including Anaphylactic reactions
- Convulsions including febrile convulsions
- Hypotonic-Hyporesponsive Episodes
- Encephalopathy/Encephalitis
- Apnea (in premature infants less than or equal to 28 weeks gestation)
- Extensive Limb Swelling

3.5.3. Missing Information

- Infants less than 6 weeks of age
- Premature infants less than 28 weeks of gestation at the time of birth
- Immunocompromised patients
- Use in children > 15 months of age

3.5.4. Signal Evaluation

No signal evaluations were completed during the PSUR reporting interval.

3.5.5. New clinical study and postmarketing data

No new significant postmarketing data were reported.

3.6. Late-breaking safety information (August 15, 2018 to November 27, 2018)

There is no important or new late-breaking information arising during this period that would alter the safety profile of VAXELIS.

4. VAXELIS Draft USPI, Section 6.2 Data from Postmarketing Experience

The sponsor proposes to include the following information in Section 6.2:

- Immune System Disorders
 - Hypersensitivity (such as rash, urticaria, dyspnea, erythema multiforme), anaphylactic reaction (such as urticaria, angioedema, edema, face edema, shock)

- General Disorders and Administration Site Conditions
 - Extensive swelling of injected limb (including swelling that involves adjacent joints).

- Nervous System
 - Seizure
 - Febrile seizure

5. LITERATURE REVIEW OF SAFETY

A PubMed search conducted on December 4, 2018, using the term “VAXELIS” did not reveal any safety issues.

6. SPONSOR’S PHARMACOVIGILANCE PLAN (PVP)

The current PVP utilizes routine surveillance; no changes to the PVP have been submitted.

The applicant does not propose any postmarketing studies.

7. OBE/DE’S ASSESSMENT

OBE/DE’s assessment is that the sponsor’s current PVP and the VAXELIS USPI, Section 6.2 Postmarketing Experience are adequate.

No new patterns of adverse events related to potential safety issues were identified in the review of literature and from all PSURs covering the period from the VAXELIS International Birthdate, February 16, 2016, to August 15, 2018. Additionally, the sponsor reports no new safety issues were identified from August 15, 2018 through November 27, 2018.

8. RECOMMENDATIONS

The current pharmacovigilance plan is adequate. Additional safety studies may be warranted if safety signals are identified during routine surveillance.