Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

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Subject: Safety and Utilization Review for the Pediatric Advisory Committee

Applicant: MSP Vaccine Company

Product: VAXELIS (Diphtheria and Tetanus Toxoids and Acellular Pertussis, Inactivated Poliovirus, Haemophilus b Conjugate and Hepatitis B Vaccine)

STN: 125563/341

Indication: Vaxelis is a vaccine indicated for active immunization to prevent diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, and invasive disease due to Haemophilus influenzae (*H. influenzae*) type b. Vaxelis is approved for use as a 3-dose series in children 6 weeks through 4 years of age (prior to the 5th birthday).

Meeting Date: Pediatric Advisory Committee Meeting, September 2023

Contents

1 INTRODUCTION

1.1 Objective

This memorandum for the Pediatric Advisory Committee (PAC) presents a comprehensive review of the postmarketing pediatric safety covering a period including 18 months following the approval in accordance with Section 505B (i) (1) of the Food and Drug Cosmetic Act [21 U.S.C. §355c]. The trigger for this pediatric postmarketing safety review was the initial approval of BLA 125563/0 on December 21, 2018 for use of Vaxelis in children 6 weeks through 4 years of age.

This memorandum documents the Food and Drug Administration's (FDA's) complete evaluation, including review of adverse event (AE) reports in passive surveillance data, periodic safety reports from the manufacturer, data mining, and a review of the published literature.

1.2 Indication and Product Description

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

Vaxelis is supplied as single-use vials of 0.5 mL volume, containing a sterile suspension for intramuscular injection. This vaccine does not contain preservatives.

1.3 Regulatory History

- December 21, 2018: Initial approval of BLA 125563/0 to for use in children 6 weeks through 4 years of age; Trigger for a previous PAC review under STN 125127/702
    - Regulatory trigger for current PAC review

2 MATERIALS REVIEWED

- Vaccine Adverse Events Reporting System (VAERS)
    - VAERS reports for Vaxelis during December 21, 2018 to May 31, 2023 (safety review period)
- Manufacturer's Submissions
    - Vaxelis U.S. package insert; updated October 19, 2022
    - Applicant response to information request regarding dose distribution data, received July 14, 2023
    - Pharmacovigilance Plan, Version
    - Periodic safety reports
- FDA Documents
    - BLA 125563/0 approval letter dated December 21, 2018

    - BLA 125563/0 Pharmacovigilance Plan Review Memorandum
- Publications (see Literature Search in Section 7)

3 LABEL CHANGES IN REVIEW PERIOD

During the safety review period, labeling supplement BLA 125563/25 was approved on May 5, 2020, to update the package insert and Patient Package Information to include revisions to *Section 6.2, Postmarketing Experience* to include Hypotonic Hyporesponsive Episode (HHE).

Section 6.2, Postmarketing Experience in the USPI lists adverse events reported during postmarketing use of Vaxelis or other vaccines containing the antigens of Vaxelis. Note that Vaxelis contains acellular pertussis antigens. HHE is a sudden onset of hypotonia, hyporesponsiveness, and pallor or cyanosis that occurs within 48 hours after childhood immunizations, has been primarily associated with pertussis containing vaccines administered to children <2 years of age. A prior review of VAERS data, showed that the majority of children (93%) with HHE received a pertussis-containing vaccine.[1] HHE is self-limited and this study reported that most (98.6%) children who experienced HHE, returned to their pre-vaccination state; median time to return was 6 hours. (Please also see discussion of HHE in section 5.1.)

4 PRODUCT UTILIZATION DATA

MSP Vaccine Company provided estimates of Vaxelis distribution data for the US and worldwide for the safety review period as follows:

- U.S. (December 21, 2018, to May 31, 2023): (b) (4) doses distributed
- Worldwide (December 1, 2018, to May 31, 2023): (b) (4) doses distributed

As per the sponsor, all distribution data are assumed to reflect administration of Vaxelis in the pediatric age group.

The sponsor also provided the following estimated number of individuals vaccinated, assuming that all doses that were distributed were also administered and that three doses were administered to each individual:

- U.S.: (b) (4) vaccinees
- Worldwide: (b) (4) vaccinees

[1] DuVernoy TS, Braun MM. Hypotonic-hyporesponsive episodes reported to the vaccine adverse event reporting system (VAERS), 1996-1998. Pediatrics. 2000 Oct;106(4):e52.

5 PHARMACOVIGILANCE PLAN AND POSTMARKETING STUDIES

5.1 Pharmacovigilance Plan

The manufacturer's original Pharmacovigilance Plan (PVP), dated December 23, 2013, lists the following important potential risks, and missing information for Vaxelis (see Table 1). There are no important identified risks in the PVP.

Table 1: Vaxelis Safety Concerns

Important Potential Risks
Hypersensitivity including anaphylactic reactions
Febrile convulsion
Hyporesponsive-hypotonic episodes
Encephalopathy/encephalitis
Apnea (in premature infants less than or equal to 28 weeks gestation)
Extensive limb swelling
Missing Information
Infants less than 6 weeks of age
Premature infants less than 28 weeks of gestation at the time of birth
Immunocompromised patients

The important potential risks with Vaxelis are labeled events in the USPI. Vaxelis is contraindicated in those with severe allergic reaction to a previous dose of Vaxelis, any ingredient of Vaxelis, or any other diphtheria toxoid, tetanus toxoid, pertussis-containing vaccine, inactivated poliovirus vaccine, hepatitis B vaccine, or Haemophilus influenzae type b vaccine. Management of acute allergic reactions, including anaphylaxis, is included in *Warnings and Precautions*. Hypersensitivity and anaphylactic reactions are also labeled under *Section 6.2 Postmarketing Experience*. Febrile seizure is labeled under *Section 6.2 Postmarketing Experience*. Hyporesponsive-hypotonic episodes (HHE) is labeled under *Warnings and Precautions*, *subsection 5.2 Adverse Reactions Following Prior Pertussis Vaccination* and under *Section 6.2 Postmarketing Experience*. Vaxelis is contraindicated in anyone with a history of encephalopathy. Apnea in premature infants is described under *Warnings and Precautions*. Extensive swelling of injected limb (including swelling that involves adjacent joints) is labeled under *Section 6.2 Postmarketing Experience*.

The important potential risks listed in Table 1 are monitored with routine safety surveillance, including review of adverse event reports submitted to FDA, manufacturer submitted periodic safety reports, published literature, and data mining. There are no postmarketing requirements or commitments (PMR/PMC) for safety-related studies or Risk Evaluation and Mitigation Strategy (REMS) for Vaxelis.

5.2 Postmarketing Studies

FDA waived the pediatric study requirement for ages less than 6 weeks and for ages 5 through 17 years because the product does not represent a meaningful therapeutic

benefit over existing therapies for pediatric patients in these age groups and is not likely to be used in a substantial number of pediatric patients in these groups.[2] Thus, there are no pediatric postmarketing studies for Vaxelis.

As mentioned in section 5.1, there are no safety-related postmarketing studies for Vaxelis.

6 ADVERSE EVENT REVIEW

6.1 Methods

The Vaccine Adverse Event Reporting System (VAERS) was queried for adverse event reports following use of Vaxelis between December 21, 2018 to May 31, 2023 (safety review period). VAERS stores postmarketing adverse events and medication errors submitted to FDA and CDC for all approved vaccines. These reports originate from a variety of sources, including healthcare providers, consumers, and manufacturers. Spontaneous surveillance systems such as VAERS are subject to many limitations, including underreporting, variable report quality and accuracy, inadequate data regarding the numbers of doses administered, and lack of direct and unbiased comparison groups. Reports in VAERS may not be medically confirmed and are not verified by FDA. FDA does not receive reports for every adverse event or medication error that occurs with a vaccine. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Also, there is no certainty that the reported event was actually due to the vaccine.

6.2 Results

The results of the VAERS search of AE reports for Vaxelis during the safety review period are listed in Table 2 below. There were total 772 reports, including 587 U.S. and 185 foreign reports, during the review period December 21, 2018 to May 31, 2023.

Table 2: Vaxelis VAERS reports during December 21, 2018 to May 31, 2023

Age	Serious Non-Fatal*		Deaths		Non-Serious		Total Reported	
	US	Foreign	US	Foreign	US	Foreign	US	Foreign
<18 years	19	58	3	0	360	0	382	58
≥ 18 years	0	0	0	0	11^	0	11	0
Unknown	5	123	0	4	189	0	194	127
All Ages	24	181	3	4	560	0	587	185

*Note: Serious non-fatal adverse events include life-threatening events, hospitalization, prolongation of hospitalization, congenital anomaly, or significant disability or otherwise medically important conditions (OMIC).
^ Reports of adult individuals who received Vaxelis in the U.S. reported that the wrong product was administered. These reports were not associated with a clinical AE.

[2] BL 125563/0 approval letter dated December 21, 2018

6.2.1 Deaths

There were 7 deaths reported during the safety review period, including 3 U.S. reports of pediatric deaths and 4 foreign reports with age unknown. Death reports were individually reviewed and are summarized below.

Pediatric death reports: 3 U.S. reports

- 2-month-old received his first set of vaccinations. Extremely irritable and fussy. Found unresponsive and declared dead 48 hours after receiving vaccination.
- 6-month-old male, received vaccination, found unresponsive and declared dead 72 hours after receiving vaccination.
- 2-month-old female, received vaccination at well-visit, found unresponsive and declared dead the next morning.

Reviewer comments: None of the above deaths were attributed to Vaxelis based on FDA review. Patients appear to have died of sudden infant death syndrome (SIDS) (see discussion below). Limited clinical details were provided in the reports.

Death reports: patient age unknown: 4 foreign reports

- Sudden infant death reported in a patient of unknown age.
- 2-month-old female reported to have a sudden infant death episode, documentation reports she had two concurrent vaccinations
- Infant of unknown age died the day after receiving vaccination. Infant also tested positive for coronavirus.
- Former premature infant of unknown age, found unresponsive and declared dead an unknown time after receiving vaccination. Patient also reported to have been septic at the time of death.

Reviewer comments: None of the above deaths were attributed to Vaxelis based on FDA review. Patients had underlying conditions and comorbidities that were contributing factors, and alternative etiologies were present. Please see below discussion regarding SIDS.

Sudden infant death syndrome [SIDS]: Some cases were attributed to Sudden infant death syndrome [SIDS], which is common in this age group, Approximately 3500 infants die annually in the United States from sleep-related infant deaths, including sudden infant death syndrome (SIDS), ill-defined deaths, and accidental suffocation and strangulation in bed.[3] Sudden unexpected infant death (SUID), also known as sudden

[3] Moon RY; TASK FORCE ON SUDDEN INFANT DEATH SYNDROME. SIDS and Other Sleep-Related Infant Deaths: Evidence Base for 2016 Updated Recommendations for a Safe Infant Sleeping Environment.

unexpected death in infancy (SUDI), is a term used to describe any sudden and unexpected death, whether explained or unexplained (including sudden infant death syndrome [SIDS] and ill-defined deaths), occurring during infancy. SIDS is the sudden unexpected death of an apparently healthy infant younger than age 12 months whose cause of death remains unknown despite a death scene investigation, a review of the clinical history, and an autopsy.[4] SIDS remains one of the leading causes of infant death in the United States. It is reported that the US SIDS rate was 40 deaths per 100,000 live births in 2013.[5] The Institute of Medicine has reviewed the topic of SIDS and concluded, "The evidence favors rejection of a causal relationship between exposure to multiple vaccines and SIDS."[6]

6.2.2 Serious Non-fatal Reports

During the safety review period, there were 24 U.S. and 181 foreign serious non-fatal reports. There were 77 reports in pediatric individuals and age was unknown in the remaining 128 reports.

The most common Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) for serious reports are displayed in Table 3. Of note, these PTs are not mutually exclusive; a single report can include multiple PTs.

Table 3: Most frequently reported PTs in serious reports

Preferred Term (PT)	# Serious Reports	Label Status *UPSI updated October 19, 2022*
Pyrexia	48	Labeled
Pallor	21	Labeled
Hyperpyrexia	20	Not labeled
Hypotonia	19	Not labeled
Vomiting	18	Labeled
Crying	17	Labeled
Seizure	16	Labeled
Diarrhea*	15	Not labeled
Cyanosis	13	Labeled[1]
Loss of Consciousness	13	Labeled[2]
Decreased Appetite	10	Labeled
Rash	10	Labeled

Note: PTs occurring with a frequency ≥10 reports are shown in above table.
* MedDRA exact term is *Diarrhoea*

[4] Goldberg N, Rodriguez-Prado Y, Tillery R, Chua C. Sudden Infant Death Syndrome: A Review. Pediatr Ann. 2018 Mar 1;47(3):e118-e123.
[5] Moon RY; TASK FORCE ON SUDDEN INFANT DEATH SYNDROME. SIDS and Other Sleep-Related Infant Deaths: Evidence Base for 2016 Updated Recommendations for a Safe Infant Sleeping Environment
[6] Immunization Safety Review: Vaccinations and Sudden Unexpected Death in Infancy. Stratton KR, Almario DA, Wizemann TM, and McCormick MC (eds). Washington, DC: National Academy Press, 2003

[1]Labeled as “pallor”
[2]Labeled as “decreased level of consciousness”

Reviewer comments: Most PTs are labeled events or consistent with a labeled event. *Hypotonia* may be related to labeled event HHE. *Hyperpyrexia* is related to labeled event *Pyrexia*. Remaining unlabeled PT, *Diarrhea*, is a non-specific event and may occur in association with multiple conditions.

6.2.3 Non-serious Reports

During the safety review period, there were 560 U.S. non-serious reports. There were 360 reports in pediatric individuals, 11 reports in adults and 189 reports with age unknown.
Note that the reports in adults were due to incorrect product administration (associated with PTs *Wrong Product Administered* or *Product Administered to Patient Of Inappropriate Age*) and most reports were not associated with a clinical adverse event.

Table 4 below lists the 10 most frequently reported PTs in non-serious reports. Of note, these PTs are not mutually exclusive; a single report can include multiple PTs.

Table 4: Most frequently reported PTs in non-serious reports

Preferred Term (PT)	# Non-serious Reports	Label Status *UPSI updated October 19, 2022*
Product Storage Error	148	Not labeled
No Adverse Event	131	Not labeled
Extra Dose Administered	67	Not labeled
Wrong Product Administered	64	Not labeled
Pyrexia	61	Labeled
Product Administered to Patient Of Inappropriate Age	47	Not labeled
Injection Site Erythema	32	Labeled
Injection Site Swelling	28	Labeled
Diarrhea*	21	Not labeled
Vomiting	20	Labeled

Note: Top 10 most frequently reported PTs are shown in above table.
* MedDRA exact term is *Diarrhoea*

Reviewer comments: Most commonly reported unlabeled PTs, in above table (*Product Storage Error, No Adverse Event, Extra Dose Administered, Wrong Product Administered*), do not represent a clinical adverse event. As mentioned earlier, a single report may contain multiple PTs. Of note, the USPI includes *Section 16 How Supplied/Storage and Handling*, which provides details on product storage, and *Section 2 Dosage and Administration* specifies the vaccination schedule and describes administration. While some of these reports may be related to administration errors, or off-label or inadvertent use in age groups not included in the USPI, these reports represent a small number of reports in the context of the global cumulative doses

distributed (more than (b) (4) doses). Other PTs are labeled events or consistent with a labeled event. Remaining unlabeled PT for *Diarrhea*, as mentioned previously, is a non-specific event and may occur in association with multiple conditions.

6.3 Data mining

Data mining was performed to evaluate whether any reported events following the use of Vaxelis were disproportionally reported compared to other vaccines in the VAERS database. The background database contains VAERS reports since 1990. Disproportionality alerts do not, by themselves, demonstrate causal associations; rather, they may serve as a signal for further investigation. A query of Empirica Signals Management with the US VAERS Vac Name run with a data lock date of June 23, 2023, for *DTAP+IPV+HIB+HEPB (VAXELIS)* identified the following PTs (displayed in Table 6) with a disproportional reporting alert (EB05>2; the EB05 refers to the lower bound of the 90% confidence interval around the Empiric Bayes Geometric Mean).

Table 5: Data mining findings

Preferred Term (PT)	# Reports	Label Status *UPSI updated October 19, 2022*
Extra dose administered	62	Not labeled
Product Storage Error	147	Not labeled

Reviewer comments: Reported unlabeled PTs do not represent a clinical adverse event (previously discussed in section 6.2.3.)

6.4 Periodic safety reports

The manufacturer's postmarketing periodic safety reports for Vaxelis were reviewed. The AEs reported were consistent with those seen in VAERS. No additional safety issues were identified, and no actions were taken by the sponsor for safety reasons.

7 LITERATURE REVIEW

A search of the US National Library of Medicine's PubMed.gov database on June 27, 2023 for peer-reviewed literature, with the search term "Vaxelis" or "DTAP-IPV-HIB-HepB vaccination" and "safety" limited by human species, and dates from PAC trigger (December 21, 2018) to date of search June 27, 2023, retrieved 1 publication pertaining to safety. No new safety concerns for Vaxelis were identified in the review of this publication, summarized in the table below:

Publication	Authors' Safety Conclusion
Wilck, MB, "Safety and immunogenicity of Vaxelis in premature infants", Hum Vaccin Immunother 2021 Jan 2;17(1):191-196.	Vaxelis' safety profile in premature infants was reassuring. The authors recommend its use.

8 CONCLUSION

This postmarketing pediatric safety review was triggered by the initial approval BLA 125563/0 on December 21, 2018 for use of Vaxelis in children 6 weeks through 4 years of age. Review of passive surveillance adverse event reports, the sponsor's periodic safety reports, and the published literature for Vaxelis does not indicate any new safety concerns. Adverse events were generally consistent with the safety data in pre-licensure studies and listed in the label. No unusual frequency, clusters, or other trends for adverse events were identified that would suggest a new safety concern.

9 RECOMMENDATIONS

FDA recommends continued routine safety monitoring of Vaxelis.