U.S. FOOD & DRUG ADMINISTRATION

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Division of Epidemiology (DE)

MEMORANDUM

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Subject: Pediatric Safety and Utilization Review for the Pediatric Advisory Committee (PAC) Meeting

Product: Bexsero®; Meningococcal Group B Vaccine

Sponsor: Glaxo SmithKline Biologicals

Application: BLA 125546/348

Indication: Active immunization to prevent invasive disease caused by *Neisseria meningitidis* group B in individuals 10 through 25 years of age

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ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
ADEM	Acute Disseminated Encephalomyelitis
aHUS	Atypical Hemolytic Uremic Syndrome
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
DE	Division of Epidemiology
EMA	European Medicines Agency
fHBP	Factor H binding protein
GBS	Guillain-Barré syndrome
GSK	GlaxoSmithKline
IND	Investigational New Drug
NadA	Neisserial adhesin A
NHBA	Neisseria Heparin Binding Antigen
OBE	Office of Biostatistics and Epidemiology
OMIC	Other Medically Important Conditions
PAER	Periodic Adverse Experience Reports
PMC	Post-Marketing Commitment
PMR	Post-Marketing Requirement
PREA	Pediatric Research Equity Act
RMP	Risk Management Plan
SIDS	Sudden Infant Death Syndrome
VAERS	Vaccine Adverse Events Reporting System
U.S.	United States

1. INTRODUCTION

1.1. Product Description

Bexsero® is an aluminum hydroxide-adjuvanted meningococcal B vaccine that contains three purified recombinant protein antigens[a] derived from *Neisseria meningitidis* group B, strain NZ 98/254. The vaccine is supplied in pre-filled syringes as a suspension for injection. It is administered as two doses, at least one month apart.

1.2. Regulatory History

The European Medicines Agency (EMA) was the first regulatory authority to approve Bexsero (January 14, 2013). The approved indication was active immunization of individuals ≥2 months of age against invasive meningococcal disease caused by *N. meningitidis* group B with age-specific schedules. On August 14, 2013, Bexsero was approved in Australia for active immunization against invasive disease caused by *N. meningitidis* group B strains in individuals ≥2 months of age. On December 6, 2013, it was approved in Canada for active immunization of individuals 2 months through 17 years of age against invasive disease caused by *N. meningitidis* group B strains.

On January 23, 2015, the Food and Drug Administration (FDA) approved Bexsero for active immunization to prevent invasive disease caused by *N. meningitidis* group B in individuals 10 through 25 years of age, under accelerated approval (21 CFR 601.40-46). Under this authority, FDA grants marketing approval on the basis of adequate and well-controlled clinical trials establishing that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. Accelerated approval was granted because, the applicant demonstrated the effectiveness of Bexsero based on its ability to induce bactericidal antibodies able to kill a panel of meningococcal serogroup B strains that are representative of prevalent strains in the US. This panel includes three strains, each of which expresses one antigen (fHbp, NadA, PorA subtype P1.4) in common with the vaccine components. This accelerated approval was contingent on post-market requirements (PMRs) to conduct two studies to confirm the breadth of coverage of Bexsero against a larger panel of genetically diverse meningococcal group B strains that represent disease isolates in the U.S.

[a] NadA (Neisserial adhesin A) as a single protein, NHBA (Neisseria Heparin Binding Antigen) and fHBP (factor H binding protein) as fusion proteins), and PorA subtype P1.4 as the main antigen of outer membrane vesicles (OMV)

Table 1. Overview of the regulatory actions taken in the U.S. since Bexsero approval

Date	Information updated (revised labeling)
October 12, 2017	Package insert to include additional adverse events of extensive limb swelling and injection nodule in Section 6.3 Postmarketing Experience
May 31, 2018	Package insert to clarify the increased risk of invasive disease caused by *N. meningitidis* group B in persons with certain complement deficiencies and persons receiving treatment that inhibits terminal complement activation (for example, eculizumab*) even if they develop serum bactericidal antibodies following vaccination with Bexsero

Source:https://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm431374.htm. Accessed on June 10, 2018
*Eculizumab (Soliris®) is a recombinant monoclonal IgG antibody and complement inhibitor indicated for the treatment of patients with Paroxysmal nocturnal hemoglobinuria, and for the treatment of atypical hemolytic uremic syndrome.
https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&applno=125166. Accessed on May 24, 2018

Prior to U.S. approval, two U.S. universities experienced unrelated meningitis B outbreaks in 2013. The Centers for Disease Control and Prevention (CDC) received permission from FDA to sponsor mass vaccination campaigns using Bexsero at those universities under an expanded access investigational new drug (IND) protocol. [1,2]

As of March 1, 2016, Bexsero had been granted marketing authorization approval in 38 countries.

1.3. CDC Advisory Committee on Immunization Practices

In February 2015, the Advisory Committee on Immunization Practices (ACIP) recommended use of meningococcal B vaccines in certain groups of persons aged ≥10 years who are at increased risk for serogroup B meningococcal disease (persons with persistent complement component deficiencies, including inherited or chronic deficiencies in C3, C5–C9, properdin, factor D, factor H, or who are taking eculizumab [Soliris®]; persons with anatomic or functional asplenia, including sickle cell disease; microbiologists routinely exposed to isolates of *N. meningitidis*; and persons identified as at increased risk because of a serogroup B meningococcal disease outbreak). In June 2015, ACIP recommended that adolescents and young adults aged 16–23 years may be vaccinated with meningococcal B vaccines to provide short-term protection against most strains of serogroup B meningococcal disease. [3]

2. OBJECTIVE

The objective of this memorandum is to present a comprehensive review of the post-marketing pediatric safety of Bexsero covering a period including 18 months following the original 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 post marketing safety review is the date of the original approval in the U.S. (January 23, 2015).

3. MATERIALS REVIEWED

Reports of adverse events following Bexsero administration and received in the Vaccine Adverse Events Reporting System (VAERS) up to December 31, 2017 were reviewed and analyzed using data mining techniques. A review of the published literature and the documents listed in Table 2 was also conducted.

Table 2. Documents reviewed

Sponsor's submissions
Bexsero US package insert https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM431447.pdf Accessed on May 16, 2018
Risk Management Plan (Version 6.0). STN#: 125546/xxx
Post-marketing Study Commitments. Annual Status Report 2018. STN#: 125546/342
Safety-Dose Distribution data for Bexsero. STN#: 125546/348
Periodic Adverse Event Report (PAER). STN#: 125546/12; 125546/18; 125546/26; 125546/56; 125546/101; 125546/117; 125546/144; 125546/168; 125546/216; 125546/256; 125546/315; 125546/336
Response to CBER's request of March 6, 2017
FDA documents
January 23, 2015 Approval Letter https://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm431446.htm Accessed on May 24, 2018
October 12, 2017 Supplement Approval Letter https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM580897.pdf Accessed on May 24, 2018
May 31, 2018 Approval letter https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM609602.pdf Accessed on June 10, 2018
FDAAA Section 915 Safety Review for Bexsero (Meningococcal Group B Vaccine)
CBER/OBE/DE Memorandum. Update language in the label section 6.3 (post-marketing experience). September 28, 2017
CBER/OVRR/DVRPA Memorandum. Prior approval supplement, Revised Bexsero Label. August 3, 2017
CBER/OBE/DE Review of Periodic Adverse Event Report (PAER). STN#: 125546/12; 125546/18; 125546/26; 125546/56; 125546/101; 125546/117; 125546/144; 125546/168; 125546/216; 125546/256; 125546/315; 125546/336

4. SAFETY-RELATED LABEL CHANGES DURING THE REVIEW PERIOD

On October 12, 2017, the sponsor revised Section 6.3, Postmarketing Experience, of the package insert to include additional adverse events, extensive limb swelling and injection nodule, based on data from the sponsor's worldwide post-marketing surveillance programs. This change was based on 170 cases of these events reported to the sponsor. These events were observed following vaccination, many

within 24 hours. Most of them occurred in infants and toddlers, lower than the age range for which Bexsero is approved for use in the U.S. There was no dose effect noted, and the events were often transient; duration of the nodule in 11 of 24 cases was less than one month.

5. U.S. PRODUCT UTILIZATION DATA

The manufacturer estimates that from January 23, 2015, through December 31, 2017, approximately 3,321,800 doses of Bexsero were distributed in the U.S. The sponsor did not have information on the amount distributed or utilized by age (i.e., in pediatric versus adult patients). Information on the actual number of people who received Bexsero is not available.

6. PHARMACOVIGILANCE PLAN AND POSTMARKETING STUDIES

6.1. Sponsor's Pharmacovigilance Plan

Table 3. Sponsor's Pharmacovigilance Plan: Important identified risks and important potential risks

Important Identified Risks	**Activities**
Fever (≥ 38.0°C)	Labeled event in PI section 6 "Solicited AEs" Continuous monitoring of spontaneous reports (routine activity)
Important Potential Risks	**Activities**
Anaphylactic reactions	Continuous monitoring of spontaneous reports (routine activity) Post licensure observational study (V72_36OB)
Guillain-Barré syndrome (GBS)	Routine pharmacovigilance with use of targeted follow-up questionnaire and adjudication Post licensure observational study (V72_36OB)
Acute Disseminated Encephalomyelitis (ADEM)	Routine pharmacovigilance with use of targeted follow-up questionnaire and adjudication Post licensure observational study (V72_36OB)
Chronic Fatigue Syndrome	Continuous monitoring of spontaneous reports (routine activity)
Kawasaki Disease (infants)	Routine pharmacovigilance with use of targeted follow-up questionnaire and adjudication Post-licensure observational safety surveillance study V72_36OB
Seizure and febrile seizure (infants and toddlers)	Routine pharmacovigilance with use of targeted follow-up questionnaire Post-licensure observational safety surveillance study V72_36OB or safety studies in Canada or Australia
Decrease of Immunogenicity secondary to prophylactic use of paracetamol (acetaminophen)	Continuous monitoring of spontaneous reports (routine activity)

Data source: Risk Management Plan (Version 6.0)

A case of anaphylaxis was reported during the CDC mass vaccination campaigns using Bexsero under an expanded access investigational new drug (IND) protocol (see sections 1.2 and 7).[1,2] No cases of Guillain-Barré syndrome (GBS), acute disseminated encephalomyelitis (ADEM), and chronic fatigue

syndrome that were considered related to Bexsero were reported in the pre-licensure clinical trials. Kawasaki disease is included in the package inserts for Bexsero in countries where Bexsero's use is approved in this age range. Seizure and febrile seizure are included in the package insert in countries where Bexsero's indication includes infants and young children. More information from VAERS reports involving seizures is provided in Section 7.4.

Table 4. Sponsor's Pharmacovigilance Plan: Important missing information

Important Missing Information	Activities
Vaccine Effectiveness	Vaccine effectiveness study (V72_38OB)
Vaccine Failure (lack of efficacy)	Routine pharmacovigilance with use of targeted follow-up questionnaire and adjudication and correlation with Meningococcal Antigen Typing System (MATS)[a] results (routine activity) Vaccine effectiveness study V72_38OB
Strain/Serotype replacement Data	Vaccine effectiveness study as first step of evaluation
Elderly Subjects	Continuous monitoring of spontaneous reports
Immuno-compromised subjects	Continuous monitoring of spontaneous reports
Chronic medical condition patients	Continuous monitoring of spontaneous reports
Safety during pregnancy or lactation	Pregnancy and lactation information included in PI Sections 8.1 and 8.3 "Use in specific populations" Continuous monitoring of spontaneous reports US pregnancy registry (V72_82OB)
Compliance in adolescent population	Continuous monitoring of spontaneous reports

Data source: Risk Management Plan (Version 6.0)

[a]Meningococcal Antigen Typing system (MATS) is an enzyme-linked immunosorbent assay (ELISA)-based system that assesses the levels of expression and immune reactivity of the three recombinant MenB-4C antigens, and estimates the susceptibility of *N. meningitidis* serogroup B isolates to killing by MenB-4C-induced antibodies. MATS data predict the susceptibility of *N. meningitidis* group B strains to killing in the human complement serum bactericidal assay (hSBA), the accepted correlate of protection for MenB-4C vaccine.[4]

Vaccine effectiveness and vaccine failure (lack of efficacy), and safety during pregnancy or lactation were included as important missing information. Additional information on effectiveness of the vaccine will be obtained as additional ongoing and planned studies are conducted (see section 6.2). The Bexsero pregnancy registry is a prospective observational study being conducted in the U.S. (section 6.2). There have been no registrants in the pregnancy registry to-date. FDA will continue to monitor the progress of the study.

6.2. Ongoing and completed studies

The Bexsero accelerated approval included two additional required post-marketing studies (studies V102_16 and V72_72) to verify and describe the clinical benefit of Bexsero. Study V102_16 (*Assess the performance of immunologic assays for evaluating the breadth of coverage against diverse Neisseria meningitides serogroup B strains*) has been completed and the results are currently under evaluation, and Study V72_72 (*Effectiveness against a panel of diverse Neisseria meningitides serogroup B strains among persons 10 through 25 years of age*) is still ongoing.

Other ongoing PMRs under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c) and post-marketing commitments are listed in tables 5 and 6, respectively.

Table 5. Postmarketing requirements under the Pediatric Research Equity Act (PREA)

Study reference number	Description	Status
V72_57	To evaluate the safety and immunogenicity of BEXSERO in North American infants 6 weeks through 12 months of age	DELAYED Revised final report submission: June 30, 2024

Table 6. Postmarketing commitments

Study reference number	Description	Status
V72_79	Safety and immunogenicity study to assess concomitant use of BEXSERO with a second dose of Meningococcal (Groups A, C, Y and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine in persons 16 years through 18 years of age	DELAYED Revised final report submission: December 30, 2021
V72_82OB	Pregnancy registry for BEXSERO in the US to prospectively collect data on spontaneously reported exposures to BEXSERO occurring within 30 days prior to the last menstrual period or at any time during pregnancy	ONGOING Final report submission: May 31, 2020

Additionally, the sponsor committed with other regulatory agencies to conduct the following postmarketing studies:

Table 7. Additional global post-marketing commitments

Study reference number	Regulatory agency	Description	Status
V72_36OB	EMA	Post-licensure observational study of safety after meningococcal B vaccine 4CMenB (Bexsero) vaccination in routine care	ONGOING Final report submission: December 31, 2019
V72_38OB	EMA	Post-licensure observational effectiveness study of meningococcal B vaccine 4CMenB (Bexsero) vaccination	ONGOING Final report submission: December 31, 2019

The completed PMR under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c) is listed in Table 8.

Table 8. Postmarketing requirements under the Pediatric Research Equity Act (PREA)

Study reference number	Description	Status
V72_28	To evaluate the safety and immunogenicity of BEXSERO in infants 2.5 months through 11 months of age and in children 2 years through 10 years of age	COMPLETED Submitted on December 30, 2015

Additionally, the sponsor committed with other regulatory agencies to conduct the following post-marketing studies that have been already completed:

Table 9. Additional global post-marketing studies

Study reference number	Regulatory agency	Description	Status
V72_75	Health Canada	A phase 3b, open label, controlled, multi-center, extension study to assess the persistence of bactericidal activity at 4 to 7.5 years after two dose primary series of Novartis Meningococcal B recombinant vaccine and the response to a third dose in adolescents and young adult subjects who previously participated in parent studies V72_41 and V72P10, compared to naïve healthy controls	COMPLETED Final report submission: September 28, 2017
V72_62	EMA	A phase IIIb, open label, Controlled, Multi-Center study to evaluate the safety, tolerability and immunogenicity of two doses of Novartis Meningococcal Group B vaccine when administered to immunocompromised patients from 2 to 17 years of age who are at increased risk of meningococcal disease because of complement deficiency or asplenia compared to matched healthy controls	COMPLETED Final report submission: February 11, 2016

7. ADVERSE EVENT REVIEW

7.1. Methods

VAERS was queried for reports of adverse events following use of Bexsero between January 23, 2015, and December 31, 2017.

VAERS stores post-marketing adverse events and medication errors submitted for all approved vaccines. These reports originate from a variety of sources, including healthcare providers, consumers, and manufacturers. A VAERS report may be assigned one or more MedDRA preferred terms (PTs).[5] Spontaneous surveillance systems such as VAERS are subject to many limitations, including underreporting, variable report quality and accuracy, inadequate data regarding the number of doses administered, and lack of direct and unbiased comparison groups.[6]

7.2. Results

The results of the VAERS search, conducted by FDA on May 29, 2018 for Bexsero during the review period, are shown below.

Table 10. Reports (consolidated events[a]) in VAERS for Bexsero for January 23, 2015 to December 31, 2017

	Deaths		Serious non-fatal[b]		Non-serious		Total	
Age (years)	**US**	**Foreign**	**US**	**Foreign**	**US**	**Foreign**	**US**	**Foreign**
<10	0	11	1	899	8	0	9	910
10-17	1	0	48	65	489	0	538	65
>18	0	0	38	46	409	0	447	46
Unknown	1	4[c]	19	372	162	0	182	376
Total	2	15	106	1382	1,068	0	1,176	1,397

[a] Duplicates have been combined into a single event.
[b] Including events designated by the manufacturer as Other Medical Important Condition (OMIC)
[c] The age of these individuals was identified through medical record review (see section 7.3)

Information about the age of patients with adverse events was reported for 78% (n=2,015) of reported events. The median age of patients involved in reported events are markedly different between U.S. reports (17.0 years) and foreign reports (1.0 year). Most events reported in the U.S. were non-serious (90.8%) and only 0.2% were reported as fatal.

7.3. Death reports

There was a total of 17 reports involving deaths; two in the U.S. and 15 outside of the U.S.

U.S. deaths

1. A 16-year-old female started treatment with eculizumab 190 days after her second dose of Bexsero. She died days after initiation of eculizumab. The autopsy diagnosis was Waterhouse-Friderichsen syndrome, which is characterized by bleeding and failure of the adrenal glands usually caused by severe meningococcal infection or other severe bacterial infection. Testing at CDC showed a non-groupable meningococcal strain, and the isolate sequence type was one that is more commonly associated with asymptomatic carriage rather than invasive disease. CDC's conclusion was that, likely as a result of increased susceptibility to meningitis due to treatment with eculizumab, the patient was infected and died from a non-groupable strain of *N. meningitidis*.[7]

2. A male of unknown age was vaccinated with Bexsero (dose number unknown). Meningitis was the reported cause of death. The reporter (consumer) did not include additional information. The manufacturer considered this case as a suspected vaccine failure.

Foreign Deaths

The 15 foreign deaths all occurred in patients less than nine years old, and 13 of them occurred in patients less than three years old.

Five of the 15 foreign deaths were reported as being death due to or following meningitis infections. These patients were all under two years of age (range 11 weeks to 15 months old). Two of these cases reported "suspected vaccine failure": (1) a nine-month-old male vaccinated with two doses of Bexsero who had meningitis serogroup B, and (2) a 15-month-old male vaccinated with two doses of Bexsero who had meningococcal sepsis, strain unknown. The remaining three death reports involving meningitis included an 18-month-old female (the strain of meningitis, the number of doses received and the interval between vaccination and symptoms onset were unknown), and an 11-week-old male diagnosed with Waterhouse-Friderichsen syndrome (PCR positive for *N. meningitidis* B serum group) and septic shock who died days after receiving the first dose of Bexsero. Autopsy revealed bilateral adrenal glands hemorrhage with consequent severe hypotensive status due to septic shock. Last, an eight-month-old male died after Bexsero vaccination with pneumococcal meningitis as the reported cause of death (no additional information was provided).

Two foreign death reports involved infections other than meningitis. These reports occurred in a 13-month-old female who died days after receiving the third dose of Bexsero with beta hemolytic streptococcal infection as the reported cause of death, and a five-year-old female who presented with gastroenteritis and fever eight days after the second dose of Bexsero. She was diagnosed with ADEM on day-15 post-vaccination, and died days later. Medical history included thrombocytopenia,

latent transient leukemia, developmental speech disorder, developmental delay, and dysmorphic syndrome. An autopsy was not performed.

Three foreign death reports involved sudden infant death syndrome (SIDS). All of them occurred in patients from two to five months old, and all patients had received multiple vaccinations in addition to Bexsero. A 19-week-old female experienced anaphylaxis after being vaccinated with the first dose of Bexsero (same day) and died the Concurrent medical conditions included an unspecified cardiac disorder. It was unknown whether an autopsy was performed. The remaining four deaths reported were of unknown causes. Three of the four cases began to have symptoms and/or died within after receiving multiple vaccinations; the fourth patient was a two-year-old male found dead days following vaccination with the second dose of Bexsero after presenting with throat pain. Concurrent conditions included middle ear inflammation and bronchial hypersensitivity.

7.4. Serious non-fatal reports

During the reporting period, there were 1,488 serious non-fatal reports to VAERS (consolidated events), including reports designated by the manufacturer as Other Medical Important Condition (OMIC). The most frequently reported MedDRA PTs in serious reports are shown in Table 11.

Table 11. Top 20 most frequently reported serious adverse events in VAERS

MedDRA PT	Total (n)	U.S. (n)	Observations
Pyrexia	391	22	Labeled
Vomiting	136	12	Consistent or synonymous with a labeled adverse event
Pallor	99	8	Consistent or synonymous with a labeled adverse event
Febrile convulsion	96	0	Reported in infants/young children outside of the U.S.[a]
Crying	88	0	Reported in infants/young children outside of the U.S.[a]
Hyperpyrexia	85	0	Reported in infants/young children outside of the U.S.[a]
Headache	72	24	Labeled
Malaise	64	8	Consistent or synonymous with a labeled adverse event
Hypotonia	63	0	Reported in infants/young children outside of the U.S.[a]
Seizure	58	3	Unlabeled event
Injection site pain	52	9	Labeled
Diarrhoea	50	8	Reported in infants/young children outside of the U.S.[a]
Loss of consciousness	50	16	Consistent or synonymous with a labeled adverse event
Pain	50	10	Labeled
Rash	46	3	Labeled
Unresponsive to stimuli	46	6	Consistent or synonymous with a labeled adverse event
Irritability	44	0	Reported in infants/young children outside of the U.S.[a]
Nausea	44	21	Labeled
Pain in extremity	44	8	Labeled
Syncope	44	11	Labeled

[a] Either all or most of the reports for these events were submitted from outside of the U.S., where Bexsero is indicated for use in individuals as young as two months of age. This age range is substantially lower than the age range (10-25 years of age) for which use is approved in the U.S. As

this adverse event is common in very young individuals, and there is no strong biologic plausibility for a causal relationship to the vaccine, these passively submitted reports are not sufficient to establish a reasonable likelihood of causality. In addition, the relevance of such safety information with respect to the U.S. indication is minimal.

Most of the frequently reported MedDRA PTs among all ages are labeled events or consistent with an already labeled event. Many of these terms are also non-specific symptoms (headache, malaise, nausea, vomiting, pain, rash) that occur frequently in a large population from numerous causes, and a causal association with Bexsero could not be established based on these passively submitted reports for these events.

Seizure is an unlabeled event in U.S. packaging, and is described in the sponsor's Pharmacovigilance Plan as an important potential risk among infants and toddlers (section 6.1). The median age of individuals with reported seizure was 0.7 years. While this PT was among the most frequent PTs among reports worldwide, there were only three U.S. serious reports with seizure as MedDRA PT, none of which were fatal. These three reports included: (1) a 19-year-old male with cerebral palsy and history of seizures; (2) a 16-year-old female with history of pseudo-seizures associated with conversion disorder; and (3) a 16-year-old female with history of "abnormal vessels in brain" (as reported by the patient's mother). Given the relatively few seizure reports in the age range for which Bexsero is used in the U.S., compared to overall use of the vaccine, and that these patients had pre-existing seizure disorders or conditions associated with seizures, these seizures are considered unlikely to have been caused by Bexsero. The seizure reports from outside of the U.S. were also individually reviewed. These reports were found to either involve febrile seizure, or involve infants or toddlers with pre-existing seizures or other neurologic conditions that could cause seizures. Many also received other vaccines in addition to Bexsero. Seizure is included in the package insert in countries where Bexsero's indication includes infants and young children (up to 10 years of age).

The eight serious non-fatal reports from the U.S. for the PT "diarrhoea" were also reviewed. The age range among those cases was 16-47 years; five individuals (62.5%) were younger than 18 years-old. Examination of the associated event terms, concomitant vaccinations, and time to onset (i.e., interval between vaccination and symptoms) in these reports did not identify a pattern suggestive of a causal relationship with Bexsero.

Among the 1,488 serious non-fatal reports (consolidated events), 106 were from the U.S.; 49 (46%) of those were reported in individuals less than 18 years of age. The pediatric adverse event experience among the age ranges receiving Bexsero in the U.S., is summarized by the most frequently reported MedDRA PTs included in U.S. serious reports among individuals ages less than 18 years in Table 12.

Table 12. Top 20 most frequently reported serious adverse events in VAERS (U.S.; ages<18years)

MedDRA PT	U.S. (n)	Total (n)	Observations
Headache	18	56	Labeled
Nausea	14	30	Labeled
Pyrexia	13	373	Labeled
Loss of consciousness	12	45	Consistent or synonymous with a labeled adverse event
Dizziness	10	26	Consistent or synonymous with a labeled adverse event
Syncope	9	41	Labeled
Dyspnea	9	32	Unlabeled event
Vomiting	8	124	Consistent or synonymous with a labeled adverse event
Pain	8	42	Labeled
Asthenia	8	30	Consistent or synonymous with a labeled adverse event
Decreased appetite	8	30	Consistent or synonymous with a labeled adverse event
Fatigue	7	24	Labeled
Chills	6	28	Consistent or synonymous with a labeled adverse event
Photophobia	6	11	Unlabeled event
Neck pain	6	10	Unlabeled event
Pallor	5	96	Consistent or synonymous with a labeled adverse event
Diarrhoea	5	44	Unlabeled event
Gait disturbance	5	38	Consistent or synonymous with a labeled adverse event
Pain in extremity	5	32	Labeled
Anaphylactic reaction	5	15	Labeled
Fall	5	11	Consistent or synonymous with a labeled adverse event
Vaccination complication	5	10	Consistent or synonymous with a labeled adverse event

Dyspnea, photophobia and neck pain are not labeled events in the U.S. U.S. serious non-fatal VAERS reports including those MedDRA PTs were either related to labeled events or signs or symptoms consistent with current labeling, contained insufficient information to reasonably suggest a causal relationship to Bexsero, or the information was sufficient and did not reasonably indicate Bexsero as the cause.

All other MedDRA PTs most frequently included in U.S. serious non-fatal reports among individuals less than 18 years of age were either labeled events or signs or symptoms consistent with current labeling.

Reports of GBS and ADEM, given that they are listed in the sponsor's Pharmacovigilance Plan as potential risks (section 6.1) were also reviewed.

Two U.S. and two foreign reports of GBS following administration of Bexsero were submitted to VAERS during the surveillance period. The U.S. cases were both reported in adults. One case was a 21-year-old female, with symptom onset one day after Bexsero vaccination, who had an upper respiratory infection two weeks before, suggested that the infection, as opposed to vaccination, may be associated with the development of GBS in this patient. The other U.S. case was reported in an 18-year-old male who presented with GBS "several weeks" after receiving the first dose of Bexsero. No additional information was available. The foreign cases were reported in a 37-year-old male who experienced GBS an "unknown time" after receiving Bexsero, and a 24-month-old female who was reportedly diagnosed with GBS less than one day after receiving the first dose of Bexsero.

VAERS contained two foreign reports for the MedDRA PT "acute disseminated encephalomyelitis,": a case occurring in a four-year-old female discussed in section 7.3 (Foreign deaths), and a case occurring in a 55-year-old female that is described in section 9 (Literature search).[8]

7.5. Non-serious reports

During the reporting period, there were 1,067 non-serious reports (consolidated events). All of them were from the U.S., and 496 (46%) were reported as occurring in individuals less than 18 years of age. The most frequently reported PTs are shown in Table 13.

Table 13. Top 20 most frequently reported adverse events included in non-serious reports

MedDRA PT	Total (n)	U.S. (n)	Observations
Injection site pain	251	251	Labeled
Injection site erythema	180	180	Labeled
Pain in extremity	161	161	Labeled
Headache	158	158	Labeled
Pyrexia	153	153	Labeled
Nausea	145	145	Labeled
Injection site swelling	144	144	Labeled
Pain	134	134	Labeled
Dizziness	130	130	Consistent or synonymous with a labeled adverse event
Fatigue	92	92	Labeled
Chills	90	90	Consistent or synonymous with a labeled adverse event
Injection site warmth	76	76	Labeled
Erythema	75	75	Labeled
Syncope	74	74	Labeled
Vomiting	60	60	Consistent or synonymous with a labeled adverse event
Injection site induration	53	53	Labeled
Injected limb mobility decreased	51	51	Consistent or synonymous with a labeled adverse event
Myalgia	49	49	Labeled
Peripheral swelling	49	49	Labeled
Loss of consciousness	44	44	Consistent or synonymous with a labeled adverse event
Urticaria	44	44	Labeled (allergic reactions)

Of note, zero non-serious foreign reports were submitted to VAERS during the surveillance period (table 10), thus, this table refers to the 20 most frequently PTs included in non-serious reports in the U.S.

All MedDRA PTs most frequently included in U.S. non-serious reports were consistent with current labeling.

7.6. Data mining

Empirical Bayesian (EB) data mining was used to identify vaccine-event combinations reported to VAERS more frequently than expected by using the Multi-Item Gamma Poisson Shrinker (MGPS) algorithm [9] in Oracle's Empirica™ Signal System. The PTs identified with a disproportional reporting alert for Bexsero (EB05≥2.0) were "injection site mass" and "vaccination complication." None of the reports of "Injection site mass" (n=33) were serious. Eight (17%) of the 46 reports of "Vaccine complication" were serious; all of them were consistent with current labeling.

Additional analyses were also restricted to serious reports for the whole database (U.S., foreign and unknown), and adjusted for age, sex, and year submitted to VAERS. In these analyses, there were no PTs with a disproportional reporting alert identified.

8. PERIODIC ADVERSE EVENT REPORTS (PAER)

In compliance with 21 CFR 600.80, the sponsor has submitted quarterly Periodic Adverse Experience Reports (PAER). No studies were initiated or discontinued for safety reasons. From the PAERs reviewed, the adverse events reported were similar to those observed in reports to VAERS and discussed above. Review of the PAER did not indicate a need for further regulatory action.

9. LITERATURE SEARCH

A literature search in PubMed was conducted on June 10, 2018, using the following search criteria "meningococcal b vaccine"[All Fields] OR "meningitis b vaccine"[All Fields] OR "serogroup b vaccine"[All Fields] OR "serogroup b vaccination"[All Fields] OR "meningococcal b vaccination"[All Fields] OR (("meningitis"[MeSH Terms] OR "meningitis"[All Fields]) AND b[All Fields] AND ("vaccination"[MeSH Terms] OR "vaccination"[All Fields])) OR "B meningococcal vaccine"[All Fields] OR "Bexsero"[All Fields] AND ("2015/01/23"[PDAT] : "2017/12/31"[PDAT]) AND English[lang].

A total of 276 publications (titles and abstracts) were identified; 21 of them included safety findings related to Bexsero:

1. Harcourt S, Morbey RA, Bates C, et al. Estimating primary care attendance rates for fever in infants after meningococcal B vaccination in England using national syndromic surveillance data. Vaccine. 2018 Jan 25;36(4):565-571

2. Velasco-Tamariz V, Prieto-Barrios M, Tous-Romero F, et al. Urticarial vasculitis after meningococcal serogroup B vaccine in a 6-year-old girl. Pediatr Dermatol. 2018 Jan;35(1):e64-e65

3. Mukherjee A, Mukherjee D, Rajai A, et al. MenB (Bexsero) immunisation side effects in extremely premature infants (<28 weeks). Arch Dis Child Fetal Neonatal Ed. 2018 Jan;103(1):F85

4. Ladhani SN, Riordan A. The yin and yang of fever after meningococcal B vaccination. Arch Dis Child. 2017 Oct;102(10):881-882

5. Parikh SR, Lucidarme J, Bingham C, et al. Meningococcal B Vaccine Failure With a Penicillin-Resistant Strain in a Young Adult on Long-Term Eculizumab. Pediatrics. 2017 Sep;140(3)

6. Nainani V, Galal U, Buttery J, et al. An increase in accident and emergency presentations for adverse events following immunisation after introduction of the group B meningococcal vaccine: an observational study. Arch Dis Child. 2017 Aug 9. pii: archdischild-2017-312941. doi: 10.1136/archdischild-2017-312941. [Epub ahead of print]

7. Kapur S, Bourke T, Maney JA, et al. Emergency department attendance following 4-component meningococcal B vaccination in infants. Arch Dis Child. 2017 Oct;102(10):899-902

8. Martinón-Torres F, Safadi MAP, Martinez AC, et al. Reduced schedules of 4CMenB vaccine in infants and catch-up series in children: Immunogenicity and safety results from a randomised open-label phase 3b trial. Vaccine. 2017 Jun 16;35(28):3548-3557

9. Duffy J, Johnsen P, Ferris M, et al. Safety of a meningococcal group B vaccine used in response to two university outbreaks. J Am Coll Health. 2017 Aug-Sep;65(6):380-388

10. Hong E, Terrade A, Taha MK. Immunogenicity and safety among laboratory workers vaccinated with Bexsero® vaccine. Hum Vaccin Immunother. 2017 Mar 4;13(3):645-648

11. Carrasco García de León SIRA, Barragán JMF. Acute disseminated encephalomyelitis secondary to serogroup B meningococcal vaccine. J Neurol Sci. 2016 Nov 15;370:53-54

12. Langley JM, MacDougall DM, Halperin BA, et al Rapid surveillance for health events following a mass meningococcal B vaccine program in a university setting: A Canadian Immunization Research Network study. Vaccine. 2016 Jul 25;34(34):4046-9

13. Audemard-Verger A, Descloux E, Ponard D, et al. Infections Revealing Complement Deficiency in Adults: A French Nationwide Study Enrolling 41 Patients. Medicine (Baltimore). 2016 May;95(19):e3548

14. Watson PS, Turner DP. Clinical experience with the meningococcal B vaccine, Bexsero(®): Prospects for reducing the burden of meningococcal serogroup B disease. Vaccine. 2016 Feb 10;34(7):875-80

15. Lee HJ, Choe YJ, Hong YJ, et al. Immunogenicity and safety of a multicomponent meningococcal serogroup B vaccine in healthy adolescents in Korea--A randomised trial. Vaccine. 2016 Feb 24;34(9):1180-6

16. Tenenbaum T, Niessen J, Schroten H. Severe Upper Extremity Dysfunction After 4CMenB Vaccination in a Young Infant.Pediatr Infect Dis J. 2016 Jan;35(1):94-6

17. Perrett KP, McVernon J, Richmond PC, et al. Immune responses to a recombinant, four-component, meningococcal serogroup B vaccine (4CMenB) in adolescents: a phase III, randomized, multicentre, lot-to-lot consistency study. Vaccine. 2015 Sep 22;33(39):5217-24

18. Esposito S, Tagliabue C, Bosis S. Meningococcal B Vaccination (4CMenB) in Infants and Toddlers. J Immunol Res. 2015;2015:402381

19. McNamara LA, Shumate AM, Johnsen P, et al. First Use of a Serogroup B Meningococcal Vaccine in the US in Response to a University Outbreak. Pediatrics. 2015 May;135(5):798-804

20. Nolan T, O'Ryan M, Wassil J, et al. Vaccination with a multicomponent meningococcal B vaccine in prevention of disease in adolescents and young adults. Vaccine. 2015 Aug 26;33(36):4437-45

21. Vesikari T, Prymula R, Merrall E, et al. Meningococcal serogroup B vaccine (4CMenB): Booster dose in previously vaccinated infants and primary vaccination in toddlers and two-year-old children. Vaccine. 2015 Jul 31;33(32):3850-8

The review of the 21 selected publications identified one event of potential interest occurring in one patient within the age range for which Bexsero is indicated in the U.S.; the case report described a vaccine failure with a penicillin-resistant meningococcal B strain in a 22-year-old female vaccinated with meningococcal ACWY vaccine and two doses of Bexsero (given one month apart), who had been diagnosed with atypical hemolytic uremic syndrome (aHUS) six months prior. At the time of the aHUS diagnosis, she had started long-term eculizumab and penicillin prophylaxis.[10] As noted in section 1.2 (Regulatory history), the package insert has been recently updated to clarify the increased risk of invasive disease caused by *N. meningitidis* group B in eculizumab recipients even if they develop serum bactericidal antibodies following vaccination with Bexsero.

A CDC publication described the safety experience of 16,974 individuals (median age: 20 years) vaccinated with at least one dose of Bexsero during a vaccination campaign conducted under IND in response to two university outbreaks (section 1.2); there were a total of three serious adverse events: a case of rhabdomyolysis requiring hospitalization was reported in a 20-year-old male who lifted weights shortly after vaccination with the second dose of Bexsero and developed fever and myalgia later that day;[1,2] a report of a case of neck stiffness, fever, myalgia, and malaise in a 18-year-old male approximately seven hours following first dose;[1] and a case of anaphylaxis in a 22-year-old female (section 6.1).[1]

The selected literature also described a case of prolonged upper extremity dysfunction, myositis, periostitis and (peri-) vasculitis in a five-month-old infant after the second injection of Bexsero in the deltoid muscle. The magnetic resonance image suggested that the injection may have been high in the deltoid muscle, which may have contributed to the development of severe symptoms.[11] There were three additional events of potential interest reported in patients outside of the age range approved in the U.S.: one case report of an urticarial vasculitis in a six-year-old female occurring seven days after Bexsero administration; [12] one case of juvenile idiopathic arthritis in an infant occurring 110 days after the third dose of Bexsero (considered as possibly related to vaccination by the study investigators) during a randomized, open-label, multi-center clinical trial (NCT01339923) that enrolled healthy infants (n=754) and children (n=404);[13] and an ADEM case in a 55-year-old woman that reported tingling sensation in the area of her left calf beginning a few hours after Bexsero administration.[8]

One publication reported increased trends of apnea, desaturations, fever, and bradycardic episodes in extremely premature infants (<28 weeks) following Bexsero introduction in the UK.[14] However, a study of Public Health England concluded that Bexsero did not increase desaturations, bradycardias and apneas in hospitalized preterm infants (median gestational age: 26.9 weeks).[15] Bexsero is not indicated in premature infants in the U.S.

All other publications reported either labeled events or signs or symptoms consistent with current labeling.

10. CONCLUSION

This post-marketing pediatric safety review was triggered by the January 23, 2015, initial approval of Bexsero. Review of passive surveillance adverse event reports, periodic safety reports, and the published literature for Bexsero does not indicate any new safety concerns. The few deaths reported could not be attributed to Bexsero, and the reported adverse events are generally consistent with the safety experience observed in pre-licensure studies and the product's package insert.

FDA will continue routine surveillance and monitoring the progress of the ongoing studies. The results of the pregnancy registry will be reviewed when available.

11. RECOMMENDATIONS

FDA recommends continued routine safety monitoring of Bexsero.

12. REFERENCES

1. Duffy J, Johnsen P, Ferris M, et al. Safety of a meningococcal group B vaccine used in response to two university outbreaks. J Am Coll Health 2017;65:380-8.
2. McNamara LA, Shumate AM, Johnsen P, et al. First Use of a Serogroup B Meningococcal Vaccine in the US in Response to a University Outbreak. Pediatrics 2015;135:798-804.
3. Meningococcal ACIP Vaccine Recommendations. 2017. (Accessed May 17, 2018, at https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/mening.html.)
4. Rajam G, Stella M, Kim E, et al. Meningococcal Antigen Typing System (MATS)-Based Neisseria meningitidis Serogroup B Coverage Prediction for the MenB-4C Vaccine in the United States. mSphere 2017;2.
5. Medical Dictionary for Regulatory Activities. (Accessed July 16, 2018, at https://www.meddra.org/.)
6. Shimabukuro TT, Nguyen M, Martin D, DeStefano F. Safety monitoring in the Vaccine Adverse Event Reporting System (VAERS). Vaccine 2015;33:4398-405.
7. Nolfi-Donegan D, Konar M, Vianzon V, et al. Fatal Nongroupable Neisseria meningitidis Disease in Vaccinated Patient Receiving Eculizumab. Emerg Infect Dis 2018;24.
8. Carrasco Garcia de Leon S, Barragan JMF. Acute disseminated encephalomyelitis secondary to serogroup B meningococcal vaccine. J Neurol Sci 2016;370:53-4.
9. DuMouchel W. Bayesian Data Mining in Large Frequency Tables, with an Application to the FDA Spontaneous Reporting System. The American Statistician 1999;53:177-90.
10. Parikh SR, Lucidarme J, Bingham C, et al. Meningococcal B Vaccine Failure With a Penicillin-Resistant Strain in a Young Adult on Long-Term Eculizumab. Pediatrics 2017;140.
11. Tenenbaum T, Niessen J, Schroten H. Severe Upper Extremity Dysfunction After 4CMenB Vaccination in a Young Infant. Pediatr Infect Dis J 2016;35:94-6.
12. Velasco-Tamariz V, Prieto-Barrios M, Tous-Romero F, Palencia-Perez SI, Postigo-Llorente C. Urticarial vasculitis after meningococcal serogroup B vaccine in a 6-year-old girl. Pediatr Dermatol 2018;35:e64-e5.
13. Martinon-Torres F, Safadi MAP, Martinez AC, et al. Reduced schedules of 4CMenB vaccine in infants and catch-up series in children: Immunogenicity and safety results from a randomised open-label phase 3b trial. Vaccine 2017;35:3548-57.
14. Mukherjee A, Mukherjee D, Rajai A, Senthil S, Edi-Osagie N. MenB (Bexsero) immunisation side effects in extremely premature infants (<28 weeks). Arch Dis Child Fetal Neonatal Ed 2018;103:F85.
15. Kent A, Beebeejaun K, Braccio S, et al. Safety of meningococcal group B vaccination in hospitalised premature infants. Arch Dis Child Fetal Neonatal Ed 2018.