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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To:	Scott Proestel, MD Director, DE, OBE, CBER
Through:	Deepa Arya, MD, MPH, MBA Branch Chief, AEB, DE, OBE, CBER
Through:	Craig Zinderman, MD, MPH Associate Director for Product Safety, DE, OBE, CBER
Subject:	Trumenba Pediatric Safety and Utilization Review for the Pediatric Advisory Committee (PAC)
Sponsor:	Wyeth Pharmaceuticals, Inc. (a subsidiary of Pfizer, Inc.)
Product:	Trumenba Meningococcal Group B Vaccine
Application:	BLA/STN 125549
Labeled Indication:	Active immunization to prevent invasive disease caused by *N. meningitidis* serogroup B. Trumenba is approved for use in individuals 10 through 25 years of age.

1. INTRODUCTION

1.1 Product Description

Trumenba, manufactured by Pfizer, Inc., is a bivalent, meningococcal vaccine that consists of two purified recombinant factor H binding proteins (fHBPs), an outer membrane lipoprotein and virulence factor that contributes to the ability of *Neisseria meningitidis* to avoid host defenses. This vaccine contains one protein antigen from each of the two fHBP subfamilies, A and B, from *Neisseria meningitidis* serogroup B. It is available in 0.5 mL single-dose pre-filled syringes and is administered via intramuscular injection.

In October, 2015, the Advisory Committee on Immunization Practices (ACIP) gave the following recommendations concerning Meningococcal Group B Vaccines (MenB)[1];

- A MenB series may be administered to adolescents and young adults aged 16–23 years to provide short-term protection against most strains of serogroup B meningococcal disease. The preferred age for MenB vaccination is 16–18 years (recommendation Category B).
- MenB vaccine should either be administered as a 3-dose series of MenB-FHbp [i.e., Trumenba] or a 2-dose series of MenB-4C [Bexsero manufactured by GSK Vaccines]. The two MenB vaccines are not interchangeable; the same vaccine product must be used for all doses.
- Vaccination should be deferred in pregnant and lactating women unless the woman is at increased risk, and, after consultation with her health care provider, the benefits of vaccination are considered to outweigh the potential risks.
- Previously, in February 2015[2], ACIP recommended routine use (recommendation Category A) of MenB vaccines in certain groups of persons at increased risk for serogroup B meningococcal disease, including during outbreaks of serogroup B meningococcal disease. College campuses that have recently experienced an outbreak of serogroup B meningococcal disease should continue to follow the recommendations for use of MenB vaccines in outbreak settings that recommend vaccination for persons aged ≥10 years.[4]

1.2 Regulatory History

Trumenba was approved by the U.S. FDA on October 29, 2014 under accelerated approval regulations, 21 CFR 601.40-46. Under these regulations, 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

[1] CDC. Use of Serogroup B Meningococcal Vaccines in Adolescents and Young Adults: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2015:64(41);1171-6.

[2] CDC. Use of serogroup B meningococcal vaccines in persons aged ≥10 years at increased risk for serogroup B meningococcal disease: recommendations of the Advisory Committee on Immunization Practices, 2015. MMWR 2015;64:608–12.

effect on a clinical endpoint other than survival or irreversible morbidity. For accelerated approval, the effectiveness of Trumenba was based on its ability to induce bactericidal antibodies that are able to kill a panel of meningococcal serogroup B strains that are representative of prevalent strains in the US. This panel includes strains that express the two fHBP variants that are expressed by the most prevalent strains causing meningococcal serogroup B disease in the US. This accelerated approval included post-market requirements (PMRs) to conduct two studies (B1971009 and B1971016) to confirm the breadth of coverage of Trumenba against a larger panel of meningococcal serogroup B strains that represent a range of genetically diverse fHBP variants in the US. The approval also included a requirement for the sponsor to conduct 3 deferred pediatric studies (B1971017, B1971035, and B1971051). These three studies will evaluate the safety and immunogenicity of Trumenba in children between the ages of 12 months and 10 years for the prevention of invasive group B meningococcal disease. Lastly, the approval included 3 studies (B1971014, B1971015, and B1971052) that the sponsor has agreed to conduct as post-market commitments (PMCs). Two of these three studies would further characterize the safety and/or immunogenicity of this vaccine, and the third is a cohort study to examine pregnancy and birth outcomes following vaccination with Trumenba.

Trumenba is indicated for active immunization to prevent invasive disease caused by *Neisseria meningitidis* serogroup B. Trumenba is approved for use in individuals 10 through25 years of age. This vaccine was initially approved as a 3-dose series at months 0, 2, and 6.[3] On April 14, 2016, FDA approved a two-dose schedule (a dose administered at 0 and 6 months) and, also, a modification of the three-dose schedule from administration at 0, 2, and 6 months to 0, 1-2, and 6 months.[4]

On March 13, 2017, the package insert was updated to include data from two confirmatory clinical studies verifying and describing the clinical benefit of the three-dose schedule (a dose administered at 0, 1-2, and 6 months) of Trumenba. The label was also updated at this time to include data from the two PMR studies B1971009 and B1971016, which confirmed effectiveness of this vaccine against a panel of diverse meningococcal group B strains.

On September 26, 2017, the package insert was updated to include two additional sections: 5.3: Limitation of Vaccine Effectiveness and 6.2: Post marketing Experience. In 5.3, the following language was added: "As with any vaccine, vaccination with Trumenba may not protect all vaccine recipients against *N. meningitidis* serogroup B infections." In section 6.2, the following was added: "The following is considered an adverse reaction for Trumenba and was reported in the post marketing experience. Because this reaction was derived from spontaneous reports, the frequency could not be determined. Immune System Disorders: Hypersensitivity reactions, including anaphylactic reactions."

[3] Trumenba Prescribing Information, Oct2014, ed.

[4] FDA. https://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm421020.htm , accessed on February 15, 2017

2. OBJECTIVE

The objective of this memorandum for the Pediatric Advisory Committee (PAC) is to present a comprehensive review of the postmarketing safety in accordance with Section 505B (i) (1) of the Food and Drug Cosmetic Act [21 U.S.C. §355c]. The two triggers for this pediatric post marketing safety review are the October 29, 2014 initial approval and the April 14, 2016 dose schedule change. This review will cover the time period of October 29, 2014 – June 30, 2017.

This memorandum documents FDA's complete evaluation, including review of adverse event reports in passive surveillance data, periodic safety reports from the manufacturer, data mining, and a review of the published literature. During the surveillance period, no new safety signals were identified and there were no reports of deaths following TRUMENBA. The product does not have a requirement for a Risk Evaluation and Mitigation Strategy (REMS) and there were no label changes regarding safety during the PAC review period (Oct 29, 2014 – Jun 30, 2017).

3. MATERIALS REVIEWED

3.1 Vaccine Adverse Events Reporting System (VAERS)
VAERS reports for Trumenba for vaccination dates Oct 29, 2014 – Jun 30, 2017

3.2 Manufacturer's Submissions

- Trumenba US package insert, dated September 2017.
- Periodic Adverse Drug Experience Report (PADER) (Quarterly from October 29, 2014, to July 23, 2017)

3.3 FDA Documents

- Trumenba Approval Letter dated Oct 29, 2014
- Trumenba Supplement Approval Letter dated Apr 14, 2016
- Trumenba Supplement Approval Letter dated Mar 13, 2017
- Trumenba Supplement Approval Letter dated Sep 26, 2017
- 915 Safety Review (dated Mar 14, 2016)

3.4 Publications (see Literature Search in section 8 and endnotes)

4. SAFETY-RELATED LABEL CHANGES IN REVIEW PERIOD

On September 26, 2017, FDA approved a revision of the package insert to add sections 5.3 and 6.2, Postmarketing Experience. Specifically, "hypersensitivity or anaphylactic reactions" were added to the Postmarketing Experience section based on spontaneous adverse event reports.

In general, hypersensitivity reactions, including anaphylactic reactions are a risk for all vaccines, and instances of hypersensitivity reactions were seen during clinical trials. The original package insert had in section 5.1, Warnings and Precautions, "epinephrine and other appropriate agents used to manage immediate allergic reactions must be immediately available should an acute anaphylactic reaction occur following administration of Trumenba." While not a new safety issue, the revision to the package insert adds information on hypersensitivity reported during postmarketing use of Trumenba.

5. PRODUCT UTILIZATION DATA

During the period of this review, October 29, 2014 through June 30, 2017, 1,461,380 doses of Trumenba were distributed in the United States. The sponsor did not have information on the amount distributed or utilized by age (i.e., in pediatric versus adult patients). No doses were distributed outside of the US during that period.

6. PHARMACOVIGILANCE PLAN AND POSTMARKETING STUDIES

6.1 Pharmacovigilance Plan

The table below summarizes Pfizer's planned pharmacovigilance activities for important potential risks and important missing information.

Table 1. Pfizer's US Pharmacovigilance Plan for Trumenba

Important Identified Risks	**Pfizer's Planned Pharmacovigilance Actions**
None	–
Important Potential Risks	**Pfizer's Planned Pharmacovigilance Actions**
Anaphylactic reactions	• Labeling • Routine Pharmacovigilance (AE reporting in accordance with 21 CFR 600.80) • Ascertain incidence rate of anaphylactic reactions in Trumenba vaccinees in ongoing Phase 2 Study 1015 and Phase 3 Studies B1971009, B1971014 & B1971016*
Important Missing Information	**Pfizer's Planned Pharmacovigilance Actions**
Vaccine effectiveness	• Collaborate with federal agencies to monitor epidemiology of invasive meningococcal disease in the US with respect to Trumenba/fHBP variants and characterization of new emerging variants, including susceptibility of any novel strains to killing by immune sera from Trumenba vaccinees
Vaccine failure	• Routine pharmacovigilance
Bactericidal response in subjects with terminal complement deficiency	• Routine Pharmacovigilance • Ascertain terminal complement deficiency status and bactericidal response of subjects in ongoing Phase 2 Study 1015 and Phase 3 Studies B1971009, B1971014 & B1971016.
Safety in pregnancy and lactation	• Observational pregnancy study using electronic health care data (Study B1971052) • Routine Pharmacovigilance • Monitor pregnancy and/or lactation status of female subjects and any SAEs among births to pregnant women exposed in ongoing Phase 2 Study 1015 and Phase 3 Studies B1971009, B1971014 & B1971016.*

*The 5 studies listed as ongoing in the PVP (Phase 2 Study 1015 and Phase 3 Studies B1971009, B1971014 & B1971016) have since been completed; anaphylaxis was not observed at an increased rate in these studies. Additionally, no additional safety concerns in pregnancy were observed in these studies.

Important Identified Risks

No specific important safety risks were identified in the clinical development program for Trumenba prior to approval. After completion of the remaining studies that were ongoing at the time of approval (Stage2 of Study B1971005 and Studies B1971009, B1971014, B1971015 and B1971016), no new safety concerns were identified.

Important Potential Risks

Anaphylactic Reactions

The potential to cause allergic reactions is common to vaccines in general, and is an important potential risk. The Warnings and Precautions section (Section 5.1) of the product label states that "epinephrine and other appropriate agents used to manage immediate allergic reactions must be immediately available should an acute anaphylactic reaction occur following administration of Trumenba."[5] In addition to labeling, the sponsor is conducting routine Pharmacovigilance and AE reporting in accordance with 21 CFR 600.80. The studies concluded since licensure consisted of an additional 10,718 subjects exposed to Trumenba and 4,497 control subjects. Among the 10,718 Trumenba vaccinees, there were 2 cases (0.02%) of anaphylaxis that were deemed by the study's principal investigator (PI) to be probably related to vaccination. Both cases resolved with treatment and there were no deaths. The sponsor continues to monitor anaphylaxis through routine pharmacovigilance as a potential risk.

Important Missing Information

Vaccine Effectiveness

Pfizer proposes population-based surveillance of the incidence of invasive meningococcal disease (IMD) (serogroup B) in collaboration with the US Centers for Disease Control and Prevention (CDC) to monitor the effectiveness of Trumenba, if it is included as part of a national age-based, routine immunization program.

Vaccine Failure

Pfizer follows spontaneous reports of lack of efficacy/effectiveness for several factors, including the frequency of occurrence, timing of the event in relation to immunization, concurrent medications, and pre-existing medical conditions.

As vaccines are generally not 100% effective, reports of lack of effect can be expected. Although the sponsor includes vaccine failure as "missing information", for the purposes of safety pharmacovigilance, vaccine effectiveness and vaccine failure are not typically considered missing information, and would thus apply to any vaccine. Additionally, since the time of approval and inclusion of these concerns in the PVP, additional information on the

[5] Trumenba Package Insert https://dailymed.nlm.nih.gov/dailymed/getFile.cfm?setid=bcaf5f75-caaf-41fd-875b-5800310070d1&type=pdf&name=bcaf5f75-caaf-41fd-875b-5800310070d1 accessed on Oct 30, 2017

effectiveness of the vaccine has been collected as part of the PMR studies and other now completed studies. Specifically, for the three-dose series, the PMR studies required under the Accelerated Approval regulations have been completed. These studies verified and described the clinical benefit attributable to Trumenba, demonstrating effectiveness against diverse meningococcal group B strains. Nonetheless, the sponsor's inclusion of lack of effect in the PVP and their planned monitoring activities are reasonable.

Bactericidal Response in patients with Terminal Complement Deficiency

Protection against invasive meningococcal disease, including serogroup B, is mediated by serum bactericidal antibodies to bacterial surface antigens. Bactericidal antibodies act in concert with human complement to kill meningococci. Persons with complement deficiencies are more susceptible to *Neisseria meningitidis* infection than complement non-deficient persons. Antibody responses to Trumenba have not been evaluated in subjects with terminal complement deficiency. Subjects with terminal complement deficiency were excluded from enrollment at United States study sites but were permitted to enroll in other countries. Results from the 5 studies completed post-licensure show that no subjects reported terminal complement deficiency as part of their medical history prior to study enrollment.

Pfizer proposes to monitor spontaneous adverse event reports (i.e., routine pharmacovigilance) for reports of lack of effect and vaccine failure in subjects with terminal complement deficiency. If safety concerns arise, risk minimization activities, such as changes to the product label, may be implemented.

Safety in Pregnancy and Lactation

Pfizer plans to conduct an observational, retrospective pregnancy study (B1971052) using electronic healthcare data and insurance claims data to assess the incidence of pregnancy outcomes (e.g., live birth, spontaneous abortion, still birth) and birth outcomes (e.g., major congenital abnormalities) following vaccination with Trumenba during pregnancy in the U.S., compared to pregnant women not exposed to Trumenba. Implementation will depend upon an adequate number of pregnant women exposed to Trumenba vaccination. Data collection for this study is ongoing and expected to end in 2022.

6.2 Completed Studies

As noted above, Trumenba was approved under accelerated approval regulations which included requirements for additional post-market studies to evaluate safety and effectiveness. Two PMRs (B1971009 and B1971016) and two additional PMC studies that were ongoing at the time of approval (B1971014 and B1971015) have since been completed. In addition, a follow-up portion (stage 2) of one additional study (B1971005) was also completed. The following Table summarizes these 5 now completed studies.

Table 2: **Completed Studies in the Trumenba Clinical Development Program since Licensure**

Study #	Study Objectives	Study Design; Population Parameters	# of Subjects	Safety Analyses Exposure (months)	Key Safety Findings*
B1971005	Safety & Immunogenicity	Phase 2, randomized, placebo-controlled study; Age (years): ≥11 to ≤18 Stage 2 (Follow-up)	536 (401 in Stage 1)	▪60µg Trumenba (0,2,6) ▪120µg Trumenba (0,2,6) ▪200µg Trumenba (0,2,6) ▪Saline (0,2,6)	▪No deaths ▪1 Related SAE (anaphylaxis)
B1971009	Safety & Immunogenicity	Phase 3, randomized, active-controlled, observer-blinded study; Age (years): ≥10 to <19	3590	▪120µg Trumenba (0,2,6), ▪Grp 1: Lot 1 ▪Grp2: Lot 2 ▪Grp3: Lot 3 ▪Grp4: HAV (0,6) + Saline (2)	▪No deaths ▪Related SAEs: None
B1971014	Safety	Phase 3, randomized, active-controlled, observer-blinded study; Age (years): ≥10 to <26	5704	▪Grp1: 120µg Trumenba (0,2,6) ▪Grp2: HAV (0,6-month) + Saline (2)	▪1 death: gunshot wound ▪2 Related SAEs in Trumenba recipients (anaphylactic reaction, neutropenia)
B1971015	Safety & Immunogenicity	Phase 2, randomized, controlled, observer-blinded study; Age (years): ≥10 to <13	2628	▪Grp1: 120µg Trumenba (0,2,6) +MCV4+Tdap (0-month) ▪Grp2: Saline (0,2,6) +MCV4+Tdap (0) ▪Grp3: 120µg Trumenba (0,2,6) +Saline+Saline (0)	▪No deaths ▪Related SAEs: None
B1971016	Safety & Immunogenicity	Phase 3, randomized, placebo-controlled, observer-blinded study; Age (years): ≥18 to	3293	▪Grp1: 120µg Trumenba (0,2,6) ▪Grp2: Saline (0,2,6)	▪3 deaths (1 suicide, 2 motor vehicle crash) ▪ 3 Related SAEs (fever, dystonia, multiple sclerosis)

Study #	Study Objectives	Study Design; Population Parameters	# of Subjects	Safety Analyses Exposure (months)	Key Safety Findings*
		<26			

*SAEs were listed as related if there was a temporal relationship following vaccination and the study investigator considered there to be a reasonable possibility that the AE was caused by the vaccine, although other etiologies could have been possible.

6.3 Ongoing Studies

There are 3 ongoing studies in children as required under the Pediatric Research Equity Act (PREA) and 2 additional post-market studies to further characterize the safety and immunogenicity of this vaccine.

Table 3: **Ongoing and Planned Studies**

Study #	Study Objectives	Study Design; Population Parameters	# of Subjects	Study Schedule/Status
B1971017*	Safety & Immunogenicity	Phase 2, randomized, active-controlled, observer-blinded study; Age: ≥24 months to <10 years	400 (enrollment complete)	Study Start: September 2014 Study Status: final report submitted 10/11/17
B1971033	Immunogenicity	Phase 3 Follow-up study Age (years): ≥11 to <19	698 (enrollment complete)	Study Start: September 7, 2012 Study Status: ongoing
B1971035*	Safety & Immunogenicity	Phase 2, randomized, active-controlled, observer-blinded study Age: ≥12 months to <18 months OR ≥18 to <24 months	Up to 396 (219 enrolled as of 3/28/16)	Study Start: May 2014 Study Status: delayed (Revised final report date: 5/31/2018)

B1971051*	Safety & Immunogenicity	Deferred pediatric study Age: 1 year to <10 years	TBD	Protocol Submission: 2/28/17 Study Completion: 11/30/19
B1971052	Examine pregnancy & birth outcomes post-Trumenba vaccination in pregnancy	Retrospective review using electronic health records	404 to 2,276 over 5 years	Study status: Protocol complete. Study Completion: 10/31/22

*Due to requirements for the Pediatric Research Equity Act (PREA)

7. ADVERSE EVENT REVIEW

7.1 Methods

The Vaccine Adverse Event Reporting System (VAERS) was queried for adverse event reports following use of Trumenba between Oct 29, 2014 and Jun 30, 2017. 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.

7.2 Results

The results of the VAERS search of adverse event reports for Trumenba during the review period are listed below.

Table 4: VAERS Reports for Trumenba (Oct 29, 2014, and Jun 30, 2017)

	Serious* Non-Fatal		**Deaths**		**Non-serious**		**Total**	
Age	**US**	**Foreign****	**US**	**Foreign**	**US**	**Foreign**	**US**	**Foreign**
<18 years	39	0	0	0	443	0	482	1
≥18 years	31	0	0	0	406	0	437	0
Unknown	9	0	0	0	271	0	280	1
Total	79	0	0	0	1,121	0	1,199	0

*Serious adverse events are defined in 21CFR600.80

**This vaccine was not licensed outside of the US during the review period.

7.2.1 Deaths

There were no death reports during this period.

7.2.2 Non-fatal serious reports

During the reporting period, there were 79 non-fatal serious reports in patients of all ages receiving this vaccine in the US. All but 2 of these cases involved patients 21 or younger. Of these, 9 reports were duplicates. The most common Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) in the remaining 70 unique reports are displayed in Table 5. Of note, these PTs are not mutually exclusive; a single report can include multiple PTs.

Table 5: Ten most frequently reported PTs for serious VAERS reports (Oct 29, 2014 to Jun 30, 2017) in patients up to age 18

MedDRA PT	Number	Labeled
Pyrexia	17	Y
Headache	12	Y
Nausea	11	Y
Chills	10	Y
Asthenia	8	-
Dizziness	8	-
Seizure	8	-
Fatigue	6	-
Hypoaesthesia	6	-
Malaise	6	-

The 8 serious reports which had the PT for seizure were all in patients who had multiple vaccinations and some underlying co-morbidities or health history which made it difficult to determine the cause.

The total number of serious reports, 79, was very small relative to the estimated 1.4 million distributed doses of the vaccine, suggesting that SAEs seem to be have been uncommon.

The most frequent PTs are currently labelled and were consistent with the most frequent SAEs seen in the clinical trials for Trumenba. These symptoms (pyrexia, headache, nausea, and chills) are also fairly non-specific; often seen after many vaccines and are unlikely to represent new safety concerns for Trumenba.

Other common PTs that were unlabeled such as dizziness, asthenia, fatigue, and malaise are likely related to syncope after vaccination, which is common after injection in general, and particularly in an adolescent population, and resolves without intervention. The number of syncopal-like events is small given the extent of vaccination. The PTs appearing in fewer than 6

reports were generally similar to labeled PTs or other common events in this population. No serious cases were reported with PTs for anaphylaxis or related events.

7.2.3 Non-serious reports

Table 3 below lists the 20 most frequently reported MedDRA preferred terms (PTs) in the 1,199 non-serious reports. Of note, these PTs are not mutually exclusive; a single report can include multiple PTs.

Table 6: ***Ten most frequently reported PTs for non-serious VAERS reports (Oct 29, 2014 to Jun 30, 2017) in patients up to age 18***

MedDRA PT	No. of Reports	Labeled
PYREXIA	156	Y
HEADACHE	145	Y
PAIN	82	Y
CHILLS	84	Y
FATIGUE	78	Y
INJECTION SITE PAIN	75	Y
NAUSEA	77	Y
PAIN IN EXTREMITY	60	Y
DIZZINESS	62	-
INJECTION SITE ERYTHEMA	57	Y

The non-serious adverse events are consistent with those seen in the pre-licensure studies and are included in the package insert.

7.3 Data mining

Data mining was performed to evaluate whether any reported events following the use of Trumenba 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 a data lock date of 11/17/2017, identified 9 PTs with a disproportional reporting alert for Trumenba (EB05>2; the EB05 refers to the lower bound of the 90% confidence interval around the Empiric Bayes Geometric Mean). Of note, these PTs are not mutually exclusive; a single report can include multiple PTs. The 9 PTs were:

Table 4. PTs Identified with Data Mining as Disproportionally Reported in VAERS (as of Nov 17, 2017)

Symptom: PT	System Organ Class	N
Liver function test abnormal	Investigations	6

Chills	General disorders	250
Headache	Nervous System	368
Myalgia	Musculoskeletal	121
Pyrexia	General disorders	410
Nausea	Gastrointestinal	231
Fatigue	General disorders	186
Malaise	General disorders	108
Influenza like illness	General disorders	41

Datamining showed that the PT liver function test abnormal had disproportional reporting. These were all reported by the same physician who provided no details and then later found the adverse event unrelated to Trumenba. The remaining PTs that were disproportionally reported coincide with labeled events and other non-serious PTs common in this age group due to syncope after vaccination.

7.4 Periodic Adverse Event Report (PAER)

The manufacturer's postmarket periodic safety reports for Trumenba covering the surveillance period were reviewed. The adverse events reported in the periodic safety reports were consistent with those seen in VAERS. No additional safety issues were identified.

8. Literature Review

A search of the US National Library of Medicine's PubMed.gov database on Dec 15, 2017, for peer-reviewed literature published between Oct 29, 2014 and Jun 30, 2017, with the search term "Trumenba" and "safety" retrieved 7 articles. The titles and abstracts of these articles were reviewed and those with the most relevant safety information are listed below. No new safety issues for Trumenba were identified in these articles.

Article	Safety Conclusion
Vesikari T, Wysocki J, Beeslaar J, et al. Immunogenicity, Safety, and Tolerability of Bivalent rLP2086 Meningococcal Group B Vaccine Administered Concomitantly With Diphtheria, Tetanus, and Acellular Pertussis and Inactivated Poliomyelitis Vaccines to Healthy Adolescents. J Pediatric Infect Dis Soc. 2016;5(2):180-7.	Trumenba was generally safe and well tolerated when given in 3 doses and when given concomitantly with DTaP/IPV. The safety and noninferiority data suggest that the administration of Trumenba + DTaP/IPV can be completed during the same office or clinic visit.
Muse D, Christensen S, Bhuyan P, et al. A Phase 2,	Trumenba given concomitantly with MCV4 + Tdap

Article	Safety Conclusion
Randomized, Active-controlled, Observer-blinded Study to Assess the Immunogenicity, Tolerability and Safety of Bivalent rLP2086, a Meningococcal Serogroup B Vaccine, Coadministered With Tetanus, Diphtheria and Acellular Pertussis Vaccine and Serogroup A, C, Y and W-135 Meningococcal Conjugate Vaccine in Healthy US Adolescents. Pediatr Infect Dis J. 2016;35(6):673-82.	was safe and non-inferior to giving MCV4 + Tdap or Trumenba alone.
Ostergaard L, Lucksinger GH, Absalon J, et al. A phase 3, randomized, active-controlled study to assess the safety and tolerability of meningococcal serogroup B vaccine bivalent rLP2086 in healthy adolescents and young adults. Vaccine. 2016;34(12):1465-71.	A study of 5,712 subjects who were randomized to Trumenba or Hep A vaccine showed that Trumenba is safe and tolerable in healthy individuals between the ages of 10 and 26.

9. CONCLUSION

This postmarketing pediatric safety review was triggered by the Oct 29, 2014 initial approval and the Apr 14, 2016 dose schedule change. Review of passive surveillance adverse event reports, periodic safety reports, and the published literature for Trumenba does not indicate any new safety concerns. Most adverse event reports were non-serious, there were no deaths reported, and the number of SAEs is small relative to the estimated use of the vaccine. The types of AEs in serious reports are generally consistent with the safety experience observed in pre-licensure studies and are already listed in the label. No pattern of adverse events was identified in serious or non-serious reports that might indicate the presence of a new safety issue. In the post-market studies completed since licensure, very few serious adverse events were observed and no new safety concerns were identified.

10. RECOMMENDATIONS

FDA recommends continued routine safety monitoring of Trumenba.

OBE will continue routine surveillance and will monitor the progress of the ongoing studies. Results of the pregnancy registry and PREA studies will be reviewed when available.