



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

PHARMACOVIGILANCE ORIGINAL BLA MEMORANDUM

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To: Goutam Sen
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Through: Manette Niu, MD
Branch Chief, AEB

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OBE, CBER, FDA

Subject: Review of Pharmacovigilance Plan

Sponsor: Pfizer

Product: TicoVac*

Application Type/Number: BLA/ STN 125740

Proposed Indication: Active immunization to prevent tick-borne encephalitis
in individuals 1 year of age and older

Submission Date: December 15, 2020

Action Due Date: August 15, 2021

*This product was also referred to as FSME-IMMUN during clinical development

1 OBJECTIVE

The purpose of this review is to assess the adequacy of the pharmacovigilance plan based on the safety profile of FSME-IMMUN.

2 PRODUCT INFORMATION

2.1 Product Description

TicoVac (tick-borne encephalitis vaccine inactivated) 0.5 mL is a sterile suspension of formaldehyde-inactivated and sucrose gradient-purified TBE virus antigen (2.4 micrograms target) obtained from chick embryo fibroblast cells. It is bound to an adjuvant (0.35 mg aluminum hydroxide, (b) (4) and diluted in a buffer system containing human serum albumin (0.5 mg). Each 0.5 mL dose contains 3.45 mg of sodium chloride, 0.22 mg of dibasic sodium phosphate, 0.045 mg of monobasic potassium phosphate, ≤ 15 mg of sucrose, and water for injection.

TicoVac (tick-borne encephalitis vaccine inactivated) 0.25 mL is a sterile suspension of formaldehyde-inactivated and sucrose gradient-purified TBE virus antigen (1.2 micrograms target) obtained from chick embryo fibroblast cells. It is bound to an adjuvant (0.17 mg aluminum hydroxide, (b) (4) and diluted in a buffer system containing human serum albumin (0.25 mg). Each 0.25 mL dose contains 1.725 mg of sodium chloride, 0.110 mg of dibasic sodium phosphate, 0.0225 mg of monobasic potassium phosphate, ≤ 7.5 mg of sucrose, and water for injection.

The vaccine is administered by intramuscular injection into the upper arm.

The primary vaccination consists of

- Three 0.25 mL doses for individuals 1 to 15 years of age;
- Three 0.5 mL doses for individuals 16 years of age and older.

2.2 Proposed indication

TicoVac is a vaccine indicated for active immunization to prevent tick-borne encephalitis (TBE) in individuals 1 year of age and older.

3 PERTINENT REGULATORY HISTORY

FSME-IMMUN has marketing authorization in 32 countries, and is marketed in 28 countries for the 0.5 mL formulation in individuals ≥ 16 years of age and in 27 countries for the 0.25 mL formulation in individuals 1 to 15 years of age. The currently licensed FSME-IMMUN adult dose (0.5 mL) first received regulatory approval on January 29, 2001 in Austria. The pediatric dose of FSME-IMMUN (0.25 mL) was licensed in Austria on December 11, 2001.

A Type C meeting was held March 5, 2019 (PS4656) to discuss the proposed regulatory package to support U.S. licensure of FSME-IMMUN. The sponsor was requested to submit a summary and analysis of spontaneous adverse event reports received since 2001, with a focus on certain adverse events (AEs) seen in the clinical trials and

reported in the post-market period. The sponsor was also requested to submit a Type 5 Master File with safety and immunogenicity data. The OBE/DE review of the summary and analysis of spontaneous adverse event reports received since 2001 may be found in MF5 (b) (4). The general format of the integrated analysis of post-market adverse events (AEs) was acceptable and the sponsor was requested to provide an updated analysis with a data lock point (DLP) near the time of the BLA submission.

4 SUMMARY OF PRIOR MARKETING EXPERIENCE

4.1 Sponsor's Analysis

The estimated cumulative worldwide unit distribution for FSME-IMMUN from launch through January 31, 2020 is estimated to be (b) (4) doses, of which approximately 30% is for FSME-IMMUN Junior. The sponsor submitted a summary and analysis of spontaneous AE reports received from January 1, 2001 through December 31, 2020. There were 19,916 cases containing 44,475 AEs through December 31, 2020. **Table 1** below lists the preferred terms (PTs) that occurred in at least 2% of reports.

Table 1. PTs that occurred in $\geq 2\%$ of spontaneous AE reports (n = 19,916 cases, data lock point December 31, 2020)

PT	Number	Percent
Inappropriate schedule of product administration	6488	32.6
Headache	2186	11.0
Pyrexia	2173	10.9
No adverse event	1560	7.8
Booster dose missed	1349	6.8
Fatigue	931	4.7
Nausea	881	4.4
Myalgia	863	4.3
Arthralgia	811	4.1
Pain in extremity	809	4.1
Dizziness	720	3.6
Incomplete course of vaccination	688	3.5
Chills	571	2.9
Paraesthesia	553	2.8
Malaise	545	2.7
Vomiting	500	2.5
Expired product administered	499	2.5
Neck pain	492	2.5
Tick-borne viral encephalitis	487	2.4
Asthenia	396	2.0

In addition, the sponsor provided case numbers and analysis of the following AEs that were seen in the clinical studies and/or reported in the post-marketing experience as a safety topic review (data lock point December 31, 2020):

- Anaphylactic Reactions: 39 cases, 23 of which the sponsor considered consistent with anaphylaxis/anaphylactoid reaction
- Autoimmune Disorders: 13 cases, 7 of which the sponsor considered consistent with the onset of autoimmune disorders
- Herpes Zoster Infections: 102 cases, 62 of which the sponsor reported as consistent with herpes zoster infection temporally associated with FSME-IMMUN
- Encephalitis: 19 cases, 9 considered by the sponsor as consistent with post-immunization encephalitis
- Convulsions (including febrile convulsions): 211 cases, 97 of which were consistent with convulsion and temporally associated with FSME-IMMU
- Neuropathy: 58 cases, 37 of which were consistent with neuropathy according to the sponsor
- Motor Dysfunction: 11 cases, 10 of which were temporally associated with vaccination
- Optic Neuritis: 22 cases, of which 11 were considered by the sponsor as optic neuritis and temporally associated
- Guillain-Barre Syndrome (GBS): 54 cases, 30 that were consistent with GBS according to the sponsor

The sponsor states these topics are adverse reactions in the Core Data Sheet.

Pregnancy and Lactation

The sponsor identified 163 cases of vaccine exposure during pregnancy (n = 138, 84.6%) or exposure to baby via lactation (n = 25, 15.3%) through a data lock point of August 31, 2020. Among the 138 cases of maternal exposure during pregnancy:

- 60 (43.5%) cases had no AE in either mother or baby.
- 48 (34.8%) cases reported no AE in mother, but did not provide information on the status of the infant.
- 30 (21.7%) reports of AEs in either the mother or infant:
 - 7 cases in which the mother experienced the following events: gestational diabetes (2 reports), respiratory disorder, pre-eclampsia, vomiting, nausea and premature labor (one report each). A healthy baby was delivered in all cases.
 - 6 reports in which the mother experienced an AE but no information was available on the infant. These were one report each of decreased fetal movement, bleeding, immune thrombocytopenia, gestational diabetes and pregnancy-induced hypertension, C-reactive protein elevation, and uterine hemorrhage.
 - There were nine reports of spontaneous abortion and one report of induced abortion.
 - There were two reports of fetal death and one report of ectopic pregnancy.

- There were four reports of AE in the baby at birth or shortly after, which were:
 - Child born with hexadactyly of all extremities and syndactyly of both hands' digit IV and V. There is a family history of syndactyly.
 - Ten-day old female who experienced cardiac arrhythmia resulting in hospitalization. The outcome is unknown.
 - Caesarean section performed at 35 weeks gestation due to pathological Doppler findings in an infant with symmetric neonatal growth retardation.
 - Infant born with cleft lip and palate.

There were 25 cases of infant exposure via lactation. There were 19 (76.0%) reports with either no experience of AE or no AE was reported. The following AEs were reported in the remaining six (24.0%) cases:

- Colic in an infant of unreported age that required hospitalization. The latency after vaccination in mother was unreported.
- Two cases of fever in breastfeeding infants of unknown age (latency was two days after mother's vaccination in one case, unreported in the other).
- Systemic rash in breastfeeding infant that occurred within an unspecified number of days after mother's vaccination.
- Two-year old male with fever and unspecified infection one day after mother's vaccination.
- Three-month old female experienced abdominal pain and projectile vomiting two days after mother's vaccination.

Reviewer comment: The sponsor's analysis of post-marketing experience does not reveal any unexpected safety concerns. The number of reported events of special interest is not higher than expected given the time this product has been in use.

4.2 FDA Analysis

A search of the Vaccine Adverse Event Reporting System (VAERS) was performed on March 9, 2021 with the following parameters:

Vaccine Type: CCE

Vaccine Name: FSME-IMMUN

Twenty-one reports were retrieved, of which eight were serious (38%). There were no death reports and 20 (95%) were foreign reports. Eighteen of the 21 cases (86%) had more than one vaccine administered. VAERS reports were individually reviewed and the following reports were considered notable:

- VAERS ID 0120509: 18 year old female received FSME-IMMUN with unspecified polio and tetanus-diphtheria vaccines. The day after vaccination, the patient developed severe balance disorder and persistent vomiting. Four weeks later, the patient experienced visual and balance disorder and acute vertigo and nystagmus. Neuritis vestibularis is suspected.

- VAERS ID 0487644: 40 year old female received a dose of “MMRVAXPRO” and FSME-IMMUN. One day after vaccination, the patient developed “central nervous disorder” with dizziness, headache, hypoesthesia, and sweating.
- VAERS ID 0545248: 17 year old male who was vaccinated with Twinrix, Stamaril, and FSME. The patient developed rash and abdominal pain the day after vaccination with elevated C-reactive protein. He was diagnosed with Henoch-Schonlein purpura.
- VAERS ID 0683598: 27 year old female vaccinated with Boostrix and FSME-IMMUN. The patient experienced acute demyelinating encephalomyelitis 61 days after vaccination.
- VAERS ID 0735825: 49 year old female received Boostrix and FSME-IMMUN and experienced myelitis 28 days after vaccination.
- VAERS ID 0782521: 30 year old male who received FSME-IMMUN and unspecified tetanus vaccine developed small fiber neuropathy 10 days after vaccination.
- VAERS ID 0825981: 8 year old female who received Twinrix and FSME-IMMUN Junior experienced anaphylaxis the day after vaccination.

Reviewer comment: There are a limited number of FSME-IMMUN reports in VAERS. Because there are no licensed TBE vaccines in the U.S., reporting of AEs associated with these vaccines is not required. Nearly all VAERS reports with FSME-IMMUN reported coadministration with another vaccine. Thus, the AEs reported cannot be solely attributed to FSME-IMMUN.

5 DESCRIPTION OF FSME-IMMUN SAFETY DATABASE

5.1 Clinical studies

This submission is supported by 11 clinical studies conducted in adults (defined as persons ≥ 16 years of age) and 12 studies conducted in children and adolescents (persons from 1 to <16 years of age). There was one study that incorporated both pediatric and adult subjects (ages ≥ 6 years). An overview of these studies is provided in **Tables 2** and **3** below.

Each protocol defined local and systemic reactions, and reporting of AEs. In most studies, subjects or their parents were asked to record local and systemic reactions in diaries after each vaccination. Queried symptoms included injection site reactions (swelling, induration, erythema, pain, tenderness, ecchymosis, and hematoma) and systemic reactions (headache, nausea, vomiting, muscle or joint pain, fatigue, malaise, and lymphadenopathy); pediatric studies also queried for loss of appetite, changes in sleeping behavior, and restlessness. Most studies measured body temperature orally or

rectally, as appropriate for the subject age, for at least 4 days after each vaccination. Other AEs were collected based on subjects reports and clinical evaluation and assessed for severity and relatedness.

Table 2. Summary of clinical studies supporting the efficacy of FSME-IMMUN in adults*

Study	Description	N
201 (Belgium)	Randomized, double blind, dose-finding safety and immunogenicity study in adults 16 to < 65 years of age. Three doses (0.6 µg, 1.2 µg, and 2.4 µg) were evaluated. Two vaccinations were administered 21 - 35 days apart.	0.6 µg = 137 1.2 µg = 133 2.4 µg = 135
202 (Belgium)	Open-label follow-up to Study 201 of the safety and immunogenicity of a third vaccination. One vaccination was administered 6 months ± 14 days after the first vaccinations in Study 201.	0.6 µg = 126 1.2 µg = 128 2.4 µg = 118
208 (Poland)	Single-blind, randomized comparison of the safety and tolerability of 5 consecutive lots of FSME-IMMUN and 2 lots of Encepur in adults 16 to < 65 years of age. Two vaccinations were administered 21 - 35 days apart.	FSME-IMMUN = 2977 Encepur = 989
213 (Poland)	Open-label follow-up to Study 208 of the safety and immunogenicity of a third vaccination. One vaccination was administered 6 months ± 14 days after the first vaccinations in Study 208.	3705 vaccinated subjects
223 (Poland)	Open-label follow-up to Study 213 to assess antibody persistence and evaluate the response to a booster vaccination of FSME-IMMUN. A booster dose of FSME-IMMUN was given 3 years ± 28 days after the 3rd TBE vaccination in Study 213.	328 vaccinated subjects
690701 (Poland)	Open-label follow-up to Study 223 to assess antibody persistence and to evaluate the response to a second booster of FSME-IMMUN. Subjects who received a booster dose in Study 223 were offered a 2nd booster dose of FSME-IMMUN if they may not have been protected against TBE for an entire further tick season at the specified time points (approximately 2, 3, 4, or 5 years after the first booster in Study 223).	32 subjects received their 2nd booster vaccination.
691101 (Pfizer Study B9371010)	Open-label follow-up study to 690701 to assess antibody persistence after a first booster and to evaluate the response to a 2nd booster vaccination. Subjects who received a first booster dose in Study 223 and did not receive a second booster dose in Study 6907010 were offered a 2nd booster dose of FSME-IMMUN if they may not have been protected against TBE for an entire further tick season at the specified time points (approximately 84, 96, 108 or 120 months after the first booster in Study 223).	15 subjects received their 2nd booster vaccination.

225 (Belgium)	Open-label, single-arm safety and immunogenicity study to establish the earliest time point at which vaccinees could be expected to show seropositive antibody levels after 2 vaccinations using a rapid immunization schedule in adults 16 to <66 years of age.	60 vaccinated subjects
690501 (Belgium)	Open-label follow-up to Study 225 to evaluate the safety and immunogenicity of a 3rd vaccination given approximately 12 months after the 2nd vaccination in Study 225.	44 enrolled subjects
690601 (Poland)	Open-label safety and immunogenicity study in two age strata (16 - 49 years and ≥50 years) when the 1st and 2nd vaccinations were administered according to a rapid schedule. Subjects received 2 vaccinations given 12 ± 2 days apart and the 3rd vaccination given approximately 6 months after the 1st dose.	170 subjects ages 16 - 49; 170 subjects ≥ 50 years
WI208682 (Austria)	Open-label, investigator-initiated study to compare the immunogenicity and reactogenicity after intramuscular versus subcutaneous vaccination in adults ages 18 - 60 who completed primary vaccination and received at least 1 booster dose at least 3 years prior to study entry.	IM: 58 SC: 58
B9371038 (Germany)	Open-label catch-up study to characterize irregularly vaccination subjects for time intervals and antibody titers. The study included children and adults ≥ 6 years who received irregular or incomplete TBE vaccination schedules. All subjects received a single booster vaccination.	2801 vaccinated subjects

*Adapted from Table 5 Clinical Overview STN125740/0, Module 2.5

Among adults (≥16 years of age), 5658 subjects received at least one dose of 2.4 µg FSME-IMMUN. An additional 137 subjects receive the formulation containing 0.6 µg of TBE antigen and 133 subjects received the formulation containing 1.2 µg of TBE in the dose-finding studies.

Table 3. Summary of clinical studies supporting the efficacy of FSME-IMMUN in children and adolescents*

Study	Description	N
197 (Austria)	Post-marketing surveillance observational safety study to observe the occurrence of fever after first vaccination in children 6 months to 12 years of age.	1922
198 (Austria)	Open-label, single-arm, safety and immunogenicity study in children 1 to <13 years of age. Two vaccinations were administered 14 to 32 days apart.	101
215 (Austria)	Open-label follow-up to Study 198 to investigate the immunogenicity and safety of a 3rd vaccination administered 9 - 10 months after the 2nd vaccination.	99
199 (Germany, Austria)	Randomized, double-blind, dose-finding study to identify the optimal dose for children 1 to <6 years of age. Three	0.3 µg = 216 0.6 µg = 215 1.2 µg = 208

	doses (0.3 µg, 0.6 µg, 1.2 µg) were evaluated. Two vaccinations were administered 21 - 35 days apart.	
206 (Germany, Austria)	Double-blind follow-up to Study 199 to evaluate the safety and immunogenicity of a 3rd vaccination with one of the three different antigen concentrations. One vaccination was administered 6 months ± 14 days after the 1st vaccination in Study 199.	0.3 µg = 211 0.6 µg = 210 1.2 µg = 204
205 (Germany)	Randomized, double-blind, dose-finding study to identify the optimal dose for children 6 to <16 years of age. Three doses (0.3 µg, 0.6 µg, 1.2 µg) were evaluated. Two vaccinations were administered 21 - 35 days apart.	0.3 µg = 206 0.6 µg = 221 1.2 µg = 212
207 (Germany)	Double-blind follow-up to Study 205 to evaluate the safety and immunogenicity of a 3rd vaccination with one of three different antigen concentrations (0.3 µg, 0.6 µg, 1.2 µg). One vaccination was administered 6 months ± 14 days after 1st vaccination in Study 205.	0.3 µg = 196 0.6 µg = 214 1.2 µg = 208
209 (Poland, Germany, Austria)	Open-label, lot consistency study to evaluate 5 consecutive lots in 3 age groups (1 - 2, 3 - 6, and 7 - 15 years). Two vaccinations were administered 21 - 35 days apart, and a 3rd vaccination administered 6 months ± 14 days after the 1st vaccination.	2417
700401 (Poland, Germany, Austria)	Open-label follow-up to Study 209 to evaluate antibody persistence after 3rd vaccination and evaluate antibody response to a booster given 36 months after 3rd vaccination.	205
700802 (Pfizer B9371021)	Open-label follow-up of Study 700401 to assess TBE antibody persistence and the immunogenicity and safety of a 2nd booster vaccination. Subjects who may not have been protected against TBE for an entire further tick season (based on relatively low TBE serum antibody levels) were offered a booster dose at either 40, 48, 60, 72, 84, 96, 108, or 120 months after 1st booster.	26
700501 (Austria)	Non-interventional study to evaluate antibody persistence approximately 3 years after a booster vaccination. Children who received 3 TBE vaccinations in Study IMAG-146A when they were 6 to 47 months of age and had received a booster vaccination approximately 3 - 4 years after the 3rd vaccination.	97
700801 (Czech Republic/Austria)	Randomized, single-blind safety, immunogenicity of 2 different TBE vaccines (FSME-IMMUN or Encepur). Children 1 to < 12 years of age were randomized 1:1. Two vaccinations were administered 28 ± 3 days apart and a 3rd vaccination administered 360 ± 14 days after the 1st vaccination.	FSME-IMMUN: 150 Encepur: 152

B9371038 (Germany)	Open-label catch-up study to characterize irregularly vaccination subjects for time intervals and antibody titers. The study included children and adults ≥ 6 years who received irregular or incomplete TBE vaccination schedules. All subjects received a single booster vaccination.	2801 vaccinated subjects
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*Adapted from Table 6 Clinical Overview STN125740/0, Module 2.5

Among pediatric and adolescent subjects (<16 years of age), 3363 received at least one 1.2 µg dose in the clinical studies. In dose-finding studies, an additional 422 subjects received the 0.3 µg formulation and 436 subjects received a 0.6 µg formulation. An additional 1899 subjects ages 6 months to 12 years were evaluated for safety after receiving half the marketed 0.5 mL dose in the post-marketing surveillance study.

5.2 Adverse events

The most frequent local reactions seen in the clinical studies of adults were injection site pain and tenderness, which did not have an association with dose or dose number. The most common systemic reactions among adults were headache, muscle pain, fatigue, and malaise. Systemic reactions tended to decrease after the second and third vaccination relative to the first.

Among pediatric subjects, fever was commonly observed in the clinical studies. Local reactions reported were injection site pain, tenderness, erythema, swelling and induration. Other than fever, common types of systemic reactions observed in pediatric subjects were appetite loss, restlessness, and sleeping disorder.

Non-fatal serious adverse events (SAEs) considered by the sponsor as not related to vaccination were reported in 28 subjects during the active phases of the 11 adult studies. An additional 47 SAEs considered unrelated to vaccination by the sponsor were reported after dose 2 of TBE vaccine in Study 208 and before dose 3 in Study 213.

Among pediatric subjects, non-fatal SAEs considered by the sponsor as not related to study vaccine were reported for 28 subjects during the active portions of the 12 pediatric studies. One SAE was considered possibly related to study vaccine for a pediatric subject enrolled in the post-marketing surveillance Study 197; this was a male subject hospitalized for a febrile convulsion two days after vaccination and was also diagnosed with rhinopharyngitis, gastroenteritis, and otitis media. There were an additional 70 pediatric subjects who experienced SAEs between the visit after the second vaccination and before the third vaccination.

There were three subjects who died among clinical trial participants for FSME-IMMUN:

- A 47 year old female in Study 213 was murdered (b) (6) days after receiving her third FSME-IMMUN vaccination.

- A one year old female died between the last visit of Study 199 and the first visit of Study 206. This participant received the 1.2 µg dose of FSME-IMMUN. She died (b) (6) days after the second vaccination due to food aspiration.
- A 32 year old female in Study 208 died (b) (4) days after the first vaccination of FSME-IMMUN. The participant lost consciousness during her daily routine. She had no vital signs upon EMS arrival and underwent resuscitation. The subject was pronounced dead on arrival to the hospital. Autopsy report attributed the direct cause of death as inflammatory changes in the cardiac muscle (interstitial myocarditis) and lungs (interstitial pneumonia). An underlying congenital heart defect of abnormal configuration and abnormal ostium of coronary vessels, and arrhythmogenic right ventricular dysplasia was found.

6 SPONSOR'S PHARMACOVIGILANCE PLAN (PVP)

The sponsor removed the important identified and potential risks as well as the important missing information from the PVP based on EMA's approach to the evaluation of risks as described in the *Guideline on good pharmacovigilance practices (GVP), Module 5 (Rev 2)* and a request from (b) (4). In a response to an Information Request submitted to STN125740/0.12 in which DE asked the sponsor for justification for the removal of all safety specifications from the PVP, the sponsor returned these safety specifications to the PVP. The sponsor's PVP is summarized in **Table 4** below.

Table 4. Sponsor's Pharmacovigilance Plan

Type of Concern	Safety Concern	Proposed Action
Identified	<ul style="list-style-type: none"> ▪ Hypersensitivity reactions, including anaphylaxis ▪ Serious neurological reactions (e.g., acute disseminated encephalomyelitis, GBS, myelitis, transverse myelitis, encephalitis, convulsions with or without fever) 	<ul style="list-style-type: none"> ▪ Routine pharmacovigilance ▪ Labeling
Potential	<ul style="list-style-type: none"> ▪ Inadequate protection in persons >60 years of age and patients with impaired immune system ▪ Precipitation and aggravation of autoimmune disorders in adults and children ▪ Administration of adult dosage in children 	<ul style="list-style-type: none"> ▪ Routine pharmacovigilance ▪ Labeling
Missing	<ul style="list-style-type: none"> ▪ Lack of safety information on pregnant or lactating women ▪ Use in patients suffering from a disease (e.g., autoimmune disease) or undergoing a form of treatment (e.g., corticosteroids) 	<ul style="list-style-type: none"> ▪ Routine pharmacovigilance ▪ Labeling

	that could be expected to influence immunological functions	
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The sponsor proposes routine pharmacovigilance for all AEs. The sponsor does not propose any additional pharmacovigilance activities or post-marketing studies.

7 ANALYSIS OF SPONSOR'S PHARMACOVIGILANCE PLAN

7.1 Important Identified Risks

7.1.1 Hypersensitivity reactions, including anaphylaxis

Hypersensitivity may occur to the vaccine active substance, excipients, or other production residues. There were no imbalances observed in the clinical studies for hypersensitivity reactions. Spontaneous reports of anaphylaxis have been infrequent considering the long post-market history for this product. The sponsor proposes routine pharmacovigilance to monitor hypersensitivity reactions. The label also contains information regarding the management of allergic reactions.

Reviewer comment: Hypersensitivity reactions and anaphylaxis are a well-recognized risk of all biologic products. The sponsor's plan for routine pharmacovigilance is adequate.

7.1.2 Serious neurological reactions (e.g., acute disseminated encephalomyelitis, GBS, myelitis, transverse myelitis, encephalitis, convulsions with or without fever)

The sponsor's analysis of post-market experience includes an evaluation of encephalitis, convulsions (including febrile), polyneuropathy, motor dysfunction, optic neuritis, and GBS (see section 4.1 above). A formal observed to expected analysis is not feasible given the limitations of postmarket reporting such as under-reporting. However, the number of cases observed appear to be below the background rates for these conditions given this product has an extensive post-market history. There were also no significant imbalances observed in the clinical studies. The sponsor proposes routine pharmacovigilance for evaluation of these safety concerns.

Reviewer comment: The sponsor's plan for routine pharmacovigilance is acceptable.

7.2 Important Potential Risks

7.2.1 Inadequate protection in persons >60 years of age and patients with impaired immune system

The sponsor included a cumulative analysis of this important potential risk in the Periodic Safety Update Report for the reporting period of February 1, 2017 through January 31, 2020. There were a total of 142 cases reporting 143 relevant events, which were:

- Vaccination failure, n = 85 (59.9%)
- Drug ineffective, n = 53 (37.3%)
- Therapeutic product drug effect decreased, n = 4 (2.8%)

The sources of these data were spontaneous reports (n = 135, 95.1%) and clinical study (n = 7, 4.9%). The events considered suggestive of an impaired immune system were: diabetes, immunosuppressant drug use, psoriasis, rheumatoid arthritis, adenocarcinoma, autoimmune thyroiditis, Basedow's disease, B-cell small lymphocytic lymphoma, chemotherapy, Crohn's disease, hepatocellular carcinoma, immunodeficiency, and multiple sclerosis. The sponsor proposes routine pharmacovigilance for this important identified risk.

Reviewer comment: As there have not been any significant safety concerns seen in the clinical trials and upon review of post-market experience, the sponsor's plan for routine pharmacovigilance is adequate.

7.2.2 Precipitation and aggravation of autoimmune disorders in adults and children

The sponsor submitted an analysis of post-market data that included an evaluation of autoimmune disorders after vaccination (see section 4.1 above). Thirteen potential cases of autoimmune disorders were identified in the post-market period. No imbalances of autoimmune disorders in the clinical trials were observed; however, patients with autoimmune diseases were excluded. The sponsor proposes routine pharmacovigilance to monitor the development and worsening of autoimmune diseases.

Reviewer comment: The sponsor's plan for routine pharmacovigilance is adequate.

7.2.3 Administration of adult dosage in children

The sponsor included a cumulative analysis of administration of adult dosage in children in the Periodic Safety Update Report for the reporting period of February 1, 2017 through January 31, 2020. The sponsor identified 708 potential cases in pediatric cases <16 years of age from the post-market period, of which 544 cases erroneously received the adult dose. The following PTs were reported in $\geq 2\%$ of cases:

- Incorrect dose administered (n = 203, 37.3%)
- Product administered to patient of inappropriate age (n = 161, 29.6%)
- Incorrect product formulation administered (n = 49, 9.0%)
- Product use issue (n = 23, 4.2%)
- Wrong product administered (n = 16, 2.9%)
- Off label use (n = 11, 2.0%)
- Overdose (n = 32, 5.9%)

There were 159 (29.2%) cases in which administration of the adult dose to pediatric patients was determined based on the patient's age and the reported adult formulation trade name. The sponsor proposes routine pharmacovigilance for this important potential risk.

Reviewer comment: It is unknown if these cases in which pediatric patients received the adult dose were associated with an AE. Given the relatively few reports seen in the context of an extensive post-market history, the sponsor's plan for routine pharmacovigilance is adequate.

7.3 Important Missing Information

7.3.1 Lack of safety information on pregnant or lactating women

The sponsor performed a post-market analysis of exposure during pregnancy and lactation (see section 4.1 above). The sponsor proposes routine pharmacovigilance to monitor for exposure during pregnancy and lactation. The labeling also notes there is limited data in pregnant and breastfeeding women.

Reviewer comment: Pregnant and lactating women are generally excluded from most clinical studies. The sponsor has relatively few reports of pregnancy and exposure during lactation given the extensive post-market experience for this product. The sponsor's analysis of post-market pregnancy exposure did not identify any safety concerns. The sponsor's plan for routine pharmacovigilance and labeling is acceptable.

7.3.2 Use in patients suffering from a disease (e.g., autoimmune disease) or undergoing a form of treatment (e.g., corticosteroids) that could be expected to influence immunological functions

Most clinical studies exclude subjects with medical conditions such as autoimmune disease or conditions requiring use of immunosuppressants. The sponsor states they have not noted a different safety profile in these subjects and proposes routine pharmacovigilance.

Reviewer comment: The sponsor's plan for routine pharmacovigilance is adequate.

8 DE ASSESSMENT

The sponsor removed all items from the safety specifications in the Risk Management Plan using EMA guidance as justification. Per FDA request, the sponsor added safety specifications to the PVP including hypersensitivity reactions (e.g., anaphylaxis) and serious neurological reactions as important identified risks. Important potential risks include inadequate protection in persons >60 years of age, patients with impaired immune system, precipitation and aggravation of autoimmune disorders in adults and children, and administration of adult dosage in children. Areas of important missing information include a lack of safety information on pregnant or lactating women, and use in patients suffering from a disease or undergoing a form of treatment that could be expected to influence immunological functions. The sponsor proposes routine pharmacovigilance and labeling to address these risks and missing information. There were no significant safety concerns from the clinical trials. Review of post-market data identified very few reports of most topics of interest, raising the possibility of significant under-reporting. However, no significant safety concerns were identified from the review of post-market data. The sponsor's safety specifications and pharmacovigilance actions are acceptable.

9 DE RECOMMENDATIONS

Should the product be approved for immunization to prevent tick-borne encephalitis in individuals one of age and older, the proposed PVP, version 1.0, dated April 12, 2021, is adequate to monitor postmarketing safety for TicoVac with routine pharmacovigilance in accordance with 21 CFR 600.80. The available safety data do not substantiate a need for a Risk Evaluation and Mitigation Strategy (REMS) or a safety-related postmarketing requirement or commitment (PMR/PMC) study. Please see the final version of the package insert submitted by the sponsor for the final agreed-upon language for the label.

**APPENDIX
Materials Reviewed**

Table A1: Materials reviewed in support of this assessment

Date	Source	Document Type	Document(s) Reviewed
December 15, 2020	Sponsor	STN125740/0	Module 1.16.1 Risk management plan
December 15, 2020	Sponsor	STN125740/0	Module 1.14.1.3 Draft labeling test
December 15, 2020	Sponsor	STN125740/0	Module 2.5 Clinical overview
December 15, 2020	Sponsor	STN125740/0	Module 2.7.4 Summary of clinical safety
December 15, 2020	Sponsor	STN125740/0	Module 5.2, Tabular listing of all clinical studies
December 15, 2020	Sponsor	STN125740/0	Module 5.3.5.1 Study reports of controlled clinical studies pertinent to the claimed indication
December 15, 2020	Sponsor	STN125740/0	Module 5.3.5.2 Study reports of uncontrolled clinical studies
December 15, 2020	Sponsor	STN125740/0	Module 5.3.5.4 Other study reports
December 15, 2020	Sponsor	STN125740/0	Module 5.3.6, Reports of postmarketing experience
December 15, 2020	Sponsor	STN125740/0	Module 1.14.1.5, Labeling History, Pregnancy and Lactation Cumulative Review
February 3, 2021	Sponsor	STN125740/0.2	Module 1.11.3 Clinical information amendment, summary and analysis of spontaneous adverse event reports received since 2001
March 26, 2021	Sponsor	STN125740/0.7	Module 1.11.3 Clinical Information Amendment, response to IR on adding safety specifications back to PVP
April 15, 2021	Sponsor	STN125740/0.12	Module 1.11.3 Clinical Information Amendment, response to IR regarding PVP safety specifications
April 15, 2021	Sponsor	STN125740/0.12	Module 1.16.1, Draft US Pharmacovigilance Plan