



**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Office of Biostatistics and Epidemiology (OBE)**

REAL WORLD EVIDENCE BLA MEMORANDUM

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To: Goutam Sen, PhD
Chair of the Review Committee
Office of Vaccines Research and Review

Through: Richard Forshee, PhD
Acting Deputy Director, OBE
CBER, FDA

Subject: Review of Priority Review Request & Package Insert

Sponsor: Pfizer Ireland Pharmaceuticals

Product: Tick Borne Encephalitis Vaccine (Whole Virus, Inactivated), Trade Name: FSME-IMMUN/TicoVac

Application Type/Number: BLA STN 125740/0

Proposed Indication: For active immunization to prevent tick-borne encephalitis (TBE) in individuals 1 year of age and older.

Submission Date: December 15, 2020

1 OBJECTIVE

The purpose of this review is to assess the adequacy of real world evidence (RWE) for Tick Borne Encephalitis Vaccine FSME-IMMUN/TicoVac.

2 PRODUCT INFORMATION

2.1 Product Description

FSME-IMMUN/TicoVac is a Pfizer whole virus inactivated tick-borne encephalitis (TBE) vaccine.

The product is administered as a series of three doses and a booster dose.

2.2 Proposed Indication

The proposed indication for the FSME-IMMUN/TicoVac in the United States (US) is for active immunization of persons against TBE in children and adults.

FSME-IMMUN/TicoVac 0.5 mL is indicated for use in individuals 16 years and older and FSME- IMMUN/TicoVac 0.25 mL is indicated for use in individuals 1 through 15 years of age.

3 REAL WORLD EFFECTIVENESS STUDIES

The Sponsor provided real world vaccine effectiveness results from field effectiveness studies in Austria. This memorandum focuses on Section 1.4.1.2 “Observational Field Studies (Real World Vaccine Effectiveness)” of the Priority Review Request, Section 14.2 “Real World Vaccine Effectiveness” of the Package Insert, and its referenced RWE articles.

Section 1.4.1.2 of the Priority Review Request: “Using data on vaccination coverage in Austria and TBE incidence rates for nonvaccinated and vaccinated populations, field effectiveness for regularly vaccinated persons for the years 2000- 2011 was calculated to be approximately 96% under worst case assumptions.”

Reviewer comment: The RWE from field effectiveness studies demonstrated high vaccine effectiveness (VE) among regularly vaccinated despite potential sources of biases.

- 1) *Regions with higher vaccination rate could have higher baseline TBE circulation, so the vaccinated population could have higher exposure to TBE virus than the unvaccinated population. This would result in a bias towards the null, so the true VE is likely higher than the observed field VE.*
- 2) *Section 1.4.1.2 of the Priority Request and Section 14.2 of the Package Insert used data in Austria between 2000 and 2011 (Heinz et al., 2013). Two TBE vaccines (FSME-Immun™ by Baxter and Encepur™ by Novartis) were available in Austria. The market coverage in Austria for FSME-Immun™ and Encepur™ was 95% and 5%, respectively in 2000, and 90% and 10%, respectively in 2006 (Heinz et al. 2007). Heinz et al. 2013 did not provide*

information about vaccine market coverage in 2011. Based on the sponsor's response to Information Request, the market coverage in Austria for FSME-Immun™ and Encepur™ was approximately 80% and 20%, respectively in 2011. This market coverage complication will not explain away the observed high VE.

- 3) Some TBE cases could not be classified unequivocally into one of the vaccination categories, and they were treated as regularly vaccinated under the worst-case assumption. This would result in a bias towards the null, so the true VE is likely higher than the observed worst-case field VE.*

Section 1.4.1.2 of the Priority Review Request: "For subjects who did not complete the regular vaccination schedule per schedule (ie, last dose given late, a worst-case protection rate of 91.3% was calculated."

Reviewer comment: *The irregularly vaccinated also showed high VE, even though the VE was significantly lower than the VE among regularly vaccinated.*

Section 1.4.1.2 of the Priority Review Request: "No statistically significant differences of vaccine effectiveness were found between the different age groups analyzed (age groups 0–15, 16–49, 50–60, and >60 years). The same holds true for subjects who have only received two doses, and not yet completed the basic immunization schedule by a third vaccination."

Section 14.2 of the Package Insert: "Vaccine effectiveness for preventing TBE was 96% to 99% overall after regular vaccination and at least as high after the first two vaccinations following the standard (b) (4) vaccination schedule."

Reviewer comment: *The following language was removed from Section 14.2 of the Package Insert "and at least as high after the first two vaccinations following the standard (b) (4) vaccination schedule"*

Section 1.4.1.2 of the Priority Review and Section 14.2 of the Package Insert used data in Austria between 2000 and 2011 (Heinz et al., 2013). However, no RWE was provided regarding vaccine effectiveness after the first two vaccinations between 2007 and 2011 because the two-doses only cohort was not included in the Heinz et al. 2013 paper. The two-doses only results between 2000 and 2006 were reported in Heinz et al. 2007 paper. The percentage of Austrian total population receiving two-doses only and following the rapid vaccination schedule was very small between 2000 and 2006. Based on TBE vaccination status data, the percentage of Austrian total population received two-doses only was 4-7% between 2000 and 2006, and only a small subset (about 5% based on 2004 data) received the second dose within 8-16 days after the first dose (rapid vaccination schedule).

In summary, the evidence in Heinz et al. 2007 article was not strong enough to support the deleted language in Section 14.2 of the Package Insert.

Section 1.4.1.2 of the Priority Review Request: “Convincing evidence for the impact of mass vaccination has been documented in Austria. In the past two to three decades, the decrease in TBE incidence in Austria is highly correlated with vaccination (Figure 1), resulting in an 84% reduction of the annual number of TBE cases, while the incidence in the unvaccinated population remained constant at approximately 6 per 100,000 population.”

Reviewer comment: The evidence was strong because the decrease in TBE cases was highly correlated with vaccination rate and incidence in unvaccinated remained constant. The market coverage complication will not explain away the observed effect.

4 OBE RWE ASSESSMENT

Even accounting for potential sources of bias within real world data, the decrease in incidence of TBE was correlated strongly with vaccination rate, and observational field studies demonstrated high vaccine effectiveness.

5 OBE RWE RECOMMENDATIONS

This real world evidence is acceptable.