## VI.2 Elements for a Public Summary

### *VI.2.1 Overview of Disease Epidemiology*

TBE (Tick-Borne Encephalitis) is a viral disease, transmitted by the bite of an infected tick, which attacks the central nervous system. It is a serious infection that can result in long-term neurological symptoms in patients, and even death. The virus can infect the membrane that surrounds the brain and spinal cord (meningitis), the brain itself (encephalitis), or both (meningoencephalitis). Following a tick bite, transmission can occur in a matter of seconds. Those infected may present with flu-like symptoms and later develop clinical signs of meningitis and/or meningoencephalitis. There is no known treatment for those infected with TBE and the only way TBE infection can be successfully prevented is through vaccination. TBE vaccination is recommended for children and adults living in endemic countries such as Austria, Finland, Germany, Hungary, Slovenia, Switzerland, Latvia, and Russia, which have national vaccination programs in place. In many countries without routine vaccination programs however, the number of TBE cases per year has remained high or increased. Globally incidence varied considerably between 1990-2007 with a high of 12,733 cases to a low of 5,462 cases. TBE morbidity also increased in Europe by almost 400% in the last 30 years between 1974 and 2003. Of those affected approximately 2.9% of children and 35%-58% of adult TBE patients suffer long-term neurological consequences, which underscore the importance of prevention. Although, TBE in childhood is thought to be a milder illness than TBE in adults, an unusually high percentage of children develop severe symptoms. Such symptoms include long lasting impairment of motor skills and concentration, with abnormal electroencephalograms (graphic record of brain waves) obtained for almost 60% of pediatric patients more than 3 years after TBEV infection. Due to the lack of antiviral treatment and the grave health consequences, TBE continues to pose a significant threat which should not be underestimated. Therefore, vaccination represents the most effective (99%) measure of protection from disease.

### *VI.2.2 Summary of Treatment Benefits*

There is no specific treatment currently available for TBE. Vaccination is the only way to prevent infection in areas where it is common. When the vaccine is administered, it triggers an immune response that is strong enough to develop immunity towards the

virus. After immunization, if subject is bitten by a tick that carries the virus, their immune system will neutralize the virus and the subject will not develop TBE.

### *VI.2.3 Unknowns relating to Treatment Benefits*

TBE vaccination has been shown to be effective in clinical studies and effective in the field. While no formal effectiveness study has been conducted, the decreasing trend in the annual number of TBE cases reported as compared to the vaccination rate in Austria in the 20 years after mass TBE vaccination that was initiated in 1978, demonstrates the effectiveness of the vaccine. Epidemiological data support the continued effectiveness of TBE vaccination with rates of 99.6% and 99.1% from 2000-2003 and 2004-2006, respectively. Of particular note, the subgroup who received the first two vaccinations at a shorter interval (approximately 5% as revealed by a survey in 2004) did not show evidence for a lower degree of protection.

### *VI.2.4 Summary of Safety Concerns*

**Important Identified Risks**

| Risk | What is Known | Preventability |
|---|---|---|
| Hypersensitivity reactions | Severe allergic reaction to egg and chick proteins<br>The container of this medicinal product contains latex rubber which may cause severe allergic reactions in persons allergic to latex. | Patients should only be vaccinated under appropriate supervision and facilities for emergency management of hypersensitivity reactions should be available.<br>Patients may use the latex free stoppers |
| Serious neurological reactions (e.g. acute disseminated encephalomyelitis, Guillain-Barré syndrome, myelitis, transverse myelitis, encephalitis, convulsions with and without fever) | Reports covering serious neurological complications are documented | In children with a history of fever convulsions or high fever following vaccinations, antipyretic prophylaxis treatment may be considered. |
| Under-dosing due to leakage from cracks in the Readyject | Complaint reports as well as pharmacovigilance reports regarding a crack or tear in the Readyject for several lots | The FSME-IMMUN Readyject syringe should be examined for a visible tear/crack in the cannula part and/or any leakage prior to the administration per DHPC where distributed<br>Per DHPC, if cracks, tears or leakage is observed, the syringe should not be used. |

## Important Potential Risks

| Risk | What is known (Including reason why it is considered a potential risk) |
|---|---|
| Inadequate protection in persons >60 years of age and patients with impaired immune system | It is known that the incidence of TBE infections in elderly over the age of 60 and those patients with impaired immune systems increases and the immune response following vaccinations might be reduced as compared to younger age groups |
| Precipitation and aggravation of autoimmune disorders in adults and children | Vaccines are suspected to be a likely “trigger” or worsening of autoimmune diseases such as multiple sclerosis, diabetes mellitus, Guillain-Barré syndrome, idiopathic thrombocytopenic purpura, and rheumatoid arthritis in persons known or suspected to have these diseases. |
| Overdose in children | Children under the age of 16 may unintentionally receive the adult formulation. |
| Interactions | There are no clinical data with respect to interactions to other vaccines and/or drugs. |

## Missing Information

| Risk | What is known |
|---|---|
| Lack of safety information on pregnant or lactating women | Given the lack of adequate data to support the use during pregnancy and the lack of information about excretion in breast milk, use of FSME-IMMUN should be considered only if it is deemed urgent to achieve TBE protection and only after careful evaluation of the risks and expected benefit. |

### *VI.2.5 Summary of Additional Risk Minimization Measures By Safety Concern*

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| Risk minimization measures(s)<br>Direct Healthcare Professional Communication letter |
| Objective and Rationale:<br>To provide awareness to healthcare professionals of the safety concern and to minimize harm to subjects that are vaccinated. |

### *VI.2.6. Planned Post Authorization Development Plan*

There are no studies in the post authorization development plan.

### *VI.2.7 Summary of changes to the Risk Management Plan over time*

| Version | Date<br>dd mm yyyy | Safety Concerns | Comment |
|---|---|---|---|
| 1.0 | 10 May 2013 | Important Identified Risks<br>• Hypersensitivity reactions, including anaphylaxis, to the active substances or any of the excipients or residues<br>• Serious neurological reactions (e.g., acute disseminated encephalomyelitis, Guillain-Barré syndrome, myelitis, transverse myelitis, encephalitis, convulsions with and without fever) | None |
| | | Important Potential Risks<br>• Inadequate protection in persons >60 years of age and patients with impaired immune system<br>• Precipitation and aggravation of autoimmune disorders in adults | None |
| | | Important Missing Information<br>• Lack of safety information on pregnant or lactating women | None |
| 1.0 update | 22 August 2013 | Important Potential risk added<br>• Overdose in Children<br>• Interactions | Response to assessment report AT/H/0123/001-002/II/38 |
| 2.0 | 29 January 2014 | Identified Risk Added<br>• Under-dosing due to leakage from cracks in the Readyject | See Module SVII |
| Update | 09 July 2014 | No change to safety concerns | Response to assessment report |
| Update | 27 October 2014 | No Changes to the safety concerns<br>RMP revisions in response to:<br>PEI:<br>Tip cap syringe timeline included in the RMP PART V: Risk minimization measures section under safety concern “Under-dosing due to leakage from cracks in the Readyject syringe” as requested.<br>AGES:<br>Part V: Effectiveness of Risk Minimization Measures in relation to important identified, potential risks and missing information, the wording | Response to PEI and AGES Additional comments |

| Version | Date<br>dd mm yyyy | Safety Concerns | Comment |
|---|---|---|---|
| | | that was deleted has been reinstated as requested. | |