PRODUCT MONOGRAPH

FSME-IMMUN[1]

Tick-Borne Encephalitis Virus Vaccine, Inactivated, with Adjuvant

2.4 µg (target value)/0.5 mL

Sterile Suspension for Intramuscular Injection

Vaccine for the Prevention of Tick-Borne Encephalitis

Manufactured by:
BAXTER AG
A-1220 Vienna, Austria

Imported and Distributed by:
BAXTER CORPORATION
Mississauga, Ontario
CANADA

Date of Revisions:
April 13, 2011

Submission Control No: 145702
Approval Date: May 19, 2011

[1] FSME-IMMUN is a trademark of Baxter AG, Vienna, Austria.

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FSME-IMMUN

Tick-Borne Encephalitis Virus Vaccine, Inactivated, with Adjuvant

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intramuscular injection, preferably into the upper arm (deltoideus muscle)	2.4 micrograms (target value) TBE virus antigen/ 0.5 mL	Aluminum hydroxide, hydrated (adjuvant) *For a complete listing see Dosage Forms, Composition and Packaging section.*

DESCRIPTION

Tick-borne encephalitis (TBE) is a viral disease with a severe acute, clinical course and considerable long-term morbidity.

FSME-IMMUN is presented as 0.5 ml suspension for injection in a pre-filled syringe.

One dose of FSME-IMMUN contains:
Tick-Borne Encephalitis Virus[1,2] (strain Neudörfl) 2.4 micrograms
[1] adsorbed on aluminium hydroxide, hydrated (0.35 milligrams Al^{3+})
[2] produced in chick embryo fibroblast cells (CEF cells)

INDICATIONS AND CLINICAL USE

FSME-IMMUN (tick-borne encephalitis virus vaccine, inactivated, with adjuvant) is indicated for the immunization against infections caused by the tick-borne encephalitis (TBE) virus of individuals 16 years and above who are at risk of contact with ticks that carry TBE virus.

The TBE virus is generally prevalent in central and northern Europe including, the East of France (Alsace), Switzerland, Southern and Central Germany (Bavaria, Baden-Württemberg, Hesse, Thuringia), Austria, North-Eastern and Central Italy, Western Hungary, Albania, Bosnia, Croatia, Serbia, Slovenia, Czech Republic, Slovakia, Poland, Denmark (Island of Bornholm), Southern Sweden, Southern Norway, Finland, Estonia, Lithuania, Latvia, Belarus, Russia and Siberia, Ukraine, Northern China, and Japan (Hokkaido) (Süss 2003). Vaccination is therefore

recommended for persons planning to travel to areas where the disease is endemic. Individuals at highest risk for contacting the disease are those planning to travel through environments where ticks are located, such as grasslands and wooded areas. These include agricultural and forestry workers, hikers, outdoor recreation enthusiasts, and Armed Forces personnel. The tick season lasts from approximately March until November, with peak tick activity occurring in the spring and summer months. In some locations, a two-peak incidence curve has been observed, with maximum activities in May/June and September/October.

CONTRAINDICATIONS

Hypersensitivity to the active component, one of the excipients, or production residues (formaldehyde, neomycin, gentamicin, protamine sulfate). Cross-allergies with aminoglycosides other than neomycin and gentamicin should be considered.

Severe hypersensitivity to egg and chick proteins (anaphylactic reaction after oral ingestion of egg protein).

Known severe hypersensitivity to latex (e.g., anaphylactic reaction/anaphylaxis). The plunger stopper of the syringe consists of chlorobutyl isoprene rubber, which contains latex proteins that may cause a severe allergic reaction in sensitized individuals.

WARNINGS AND PRECAUTIONS

FSME-IMMUN is not intended for use in children and adolescents up to 16 years of age.

Serious Warnings and Precautions

As with all vaccines administered by injection, allergic reactions, including severe anaphylactic reactions (such as anaphylactic shock), may occur after administration of FSME-IMMUN. Immediate emergency treatment should always be readily available. Non-severe allergy to egg protein does not usually constitute an absolute contraindication to vaccination with FSME-IMMUN. Nevertheless, such persons should only be vaccinated under appropriate supervision and facilities for emergency management of hypersensitivity reactions should be available.

The levels of potassium and sodium are at less than 1 mmol per dose, i.e. essentially “potassium and sodium-free”.

In particular, after the first vaccination, fever may occur in rare cases. Fever generally subsides within 24 hours. Antipyretic treatment should be initiated whenever warranted.

In the case of a tick-bite between the first and second vaccinations with FSME-IMMUN (inactivated tick-borne encephalitis virus vaccine, adjuvanted), prevention of infection with TBE virus cannot be expected.

As with all vaccines, FSME-IMMUN may not completely protect all subjects receiving the vaccine against the infection that it is intended to prevent.

The appearance of clinical signs and symptoms suggestive of a possible TBE infection in a subject receiving the vaccine should be thoroughly investigated for the possibility of alternative causes. Tick bites may transmit infections other than TBE, including certain pathogens that can sometimes cause a clinical picture that resembles TBE.

TBE vaccines do not provide protection against Borrelia infection.

General

For the development of protective immunity, the number of doses and time intervals between injections should strictly be adhered to. Extending the interval between the three doses may leave subjects with inadequate protection against infection in the interim period.

Vaccination should be postponed in patients with acute clinical conditions (with or without fever) that could be aggravated by adverse reactions to the vaccine or could impair the interpretation of possible adverse reactions to the vaccine.

Caution is required when considering the need for vaccination in persons with pre-existing cerebral disorders such as active demyelinating disorders or poorly controlled epilepsy.

Special Populations

Pregnant Women:

The safety of FSME-IMMUN for use in human pregnancy has not been established in clinical trials. Therefore, FSME-IMMUN should only be given with caution to pregnant women after careful, individual consideration of potential risks and benefits.

Nursing Women:

The safety of FSME-IMMUN for use in lactation has not been established in clinical trials. Therefore, FSME-IMMUN should only be given with caution to breast-feeding mothers after careful, individual consideration of potential risks and benefits.

Pediatrics:

FSME-IMMUN is not to be used in children up to 16 years of age.

Geriatrics (> 60 years of age) and persons with impaired immune system (including those undergoing immunosuppressive therapy):

Immune response to TBE vaccination may be lower in older people and persons with impaired immune system. In the elderly, antibody concentrations achieved by vaccination tend to decline more rapidly. There is no clinical data on which to base dose recommendations for subjects older than 60 years of age and persons with impaired immune system. Therefore consideration may be given to determining the antibody concentration at four weeks after the second dose and administering an additional dose if there is no evidence of seroconversion at this time. The originally planned third dose should be given as scheduled, and the need for subsequent booster doses may then be assessed by serological tests at intervals. The first booster dose should be given no more than 3 years after the third dose. Subsequent booster doses should be given following official recommendations, but not less than 3 years after the last booster dose.

Individuals with autoimmune disorders:

In the case of known or suspected autoimmune disease, the risk of a possible infection with tick-borne encephalitis must be weighed against the risk of an unfavorable influence of the vaccination on the autoimmune disease.

Monitoring and Laboratory Tests

Whenever serological testing is considered necessary in order to determine the need for sequential doses, assays should be performed in an experienced, qualified laboratory. This is because cross reactivity with pre-existing antibodies due to natural exposure or previous vaccination against other flaviviruses (e.g. Japanese encephalitis, Yellow fever, Dengue virus) may give false positive results.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

FSME-IMMUN (tick-borne encephalitis virus vaccine, inactivated, with adjuvant) is generally well tolerated. The safety of the vaccine has been assessed in clinical trials, and by post-market surveillance.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

For adults, the frequencies have been calculated based on a pooled analysis of adverse events from 7 clinical studies conducted with FSME-IMMUN 0.5 mL (2.4 mcg) in subjects aged 16 or

older receiving 3 vaccinations (3512 subjects after the first vaccination, 3477 after the second vaccination, and 3274 after the third vaccination). The frequencies were pooled and presented on all three vaccinations not on a per patient basis.

Table 1: Undesirable effects (ADR Term MedDRA version 13.0)				
System organ class	**Frequency**			
	Very common: ≥10%	**Common: ≥1% and <10%**	**Uncommon: ≥0.1% and <1%**	**Rare: ≥0.01% and <0.1%**
Blood and lymphatic system disorders			Lymphadenopathy	
Immune system disorders				Hypersensitivity
Nervous system disorders		Headache		Somnolence
Ear and labyrinth disorders				Vertigo[a]
Gastrointestinal disorders		Nausea	Vomiting	Diarrhoea Abdominal pain
Musculosceletal and connective tissue disorders		Myalgia Arthalgia		
General disorders and administration site conditions	Injection and infusion site reactions[b] (e.g., Injection site pain)	Fatigue Malaise	Pyrexia (Injection site hemorrhage)	Injection site erythema, Injection site induration, Injection site swelling, Injection site pruritus, Injection site paresthesia, Injection site warmth)

[a] The frequency of vertigo is based on the rate reported only after the first vaccination (n = 3512). Vertigo was not reported after the second or third vaccinations.
[b] A subject may have experienced more than 1 event.

Post-Market Adverse Drug Reactions

The following additional undesirable effects were reported under the spontaneous reporting system, listed by MedDRA (version 13.0) System Organ Class (SOC), then by Preferred Term:

Infections and infestations:
Herpes zoster (triggered in pre-exposed patients)

Immune system disorders:
Anaphylactic reaction and precipitation or aggravation of autoimmune disease (e.g., Multiple sclerosis)

Nervous system disorders:
Demyelination (acute disseminated encephalomyelitis), Guillain Barré syndrome, myelitis, myelitis transverse, sensory disturbance and motor dysfunction (neuralgia, optic neuritis), mening-

ism, dizziness, convulsion, encephalitis, sensory abnormalities and motor dysfunctions (facial palsy/facial paresis, paralysis/paresis, neuritis dysesthesia, hypoesthesia, paresthesia), aseptic meningitis

Cardiac disorders:
Tachycardia

Eye disorders:
Visual disorders, photophobia, eye pain

Ear and labyrinth disorders:
Tinnitus

Respiratory, thoracic, and mediastinal disorders:
Dyspnea

General disorders and administration site conditions:
Asthenia, chills, gait disturbances, influenza-like illness, oedema, injection site joint movement impairment, injection site joint pain, injection site nodule, injection site inflammation

Musculo-skeletal, connective tissue and bone disorders:
Neck pain, musculoskeletal stiffness (including neck stiffness), pain in extremity, back pain, joint swelling

Skin and subcutaneous tissue disorders:
Urticaria, rash erythematous, rash maculo-papular, pruritus, erythema, hyperhidrosis, dermatitis

DRUG INTERACTIONS

Overview

No Interaction studies with vaccines or medicinal products have been performed.

Drug-Drug Interactions

The administration of other vaccines at the same time as FSME-IMMUN should be performed only in accordance with official recommendations. If other injectable vaccines are to be given at the same time, administrations should be into separate sites and, preferably, into separate limbs.
A protective immune response may not be elicited in persons undergoing immunosuppressive therapy or persons with an impaired immune system (for vaccination schedule please see section "Recommended Dose and Dosage Adjustment"). There is no specific clinical data on which to base dose recommendations in such patients.

Drug-Laboratory Interactions

Cross reactivity with pre-existing antibodies due to natural exposure or previous vaccination against other flaviviruses (e.g. Japanese encephalitis, Yellow fever, Dengue virus) may give false positive results.

Drug-Lifestyle Interactions

FSME-IMMUN is unlikely to affect a person's ability to drive and use machines. It should be taken into account, however, that impaired vision or dizziness may occur.

DOSAGE AND ADMINISTRATION

Dosing Considerations

The primary vaccination schedule is the same for all persons from the age of 16 onwards and consists of three doses of FSME-IMMUN.

The first dose should be given on an elected date and the second dose should be given between 1 and 3 months later. The third dose should be given between 5 and 12 months after the second vaccination. If there is a need to achieve an immune response rapidly, the second dose may be given two weeks after the first dose.

Recommended Dose and Dosage Adjustment

Recommended dosage for FSME-IMMUN (tick-borne encephalitis virus vaccine, inactivated, with adjuvant) is summarized in the following table:

VACCINATION SCHEDULE

Basic Immunization	**Dose**	**Interval**
1st dose	0.5 mL i.m.	-
2nd dose	0.5 mL i.m.	1 to 3 months after the 1st vaccination
3rd dose	0.5 mL i.m.	5 to 12 months after the 2nd vaccination
Rapid Immunization Schedule	**Dose**	**Interval**
1st dose	0.5 mL i.m.	-
2nd dose	0.5 mL i.m.	2 weeks after the 1st vaccination
3rd dose	0.5 mL i.m.	5 to 12 months after the 2nd vaccination

To achieve immunity before the beginning of the seasonal tick activity, which is in spring, the first and second doses should preferably be given in the winter months. The vaccination schedule should ideally be completed with the third vaccination within the same tick season or at the least before the start of the following tick season.

For persons with an impaired immune system (including those undergoing immunosuppressive therapy) and elderly persons (above the age of 60):

There are no specific clinical data on which to base dose recommendations. However, consideration may be given to determining the antibody concentration at four weeks after the second dose and administering an additional dose if there is no evidence of seroconversion at this time. A third dose should be given as scheduled and the need for subsequent booster doses may then be assessed by serological tests at intervals.

Booster doses

Persons from 16 to 60 years of age

The first booster dose should be given 3 years after the third dose.
Sequential booster doses should be given following official recommendations. Based on local epidemiology and experience, intervals of 3 up to 5 years for sequential boosters have been officially recommended.

Persons above 60 years of age

In general, in individuals over 60 years of age the booster intervals should not exceed three years.

Alternatively, before giving a booster vaccination, the antibody concentration may be assessed using enzyme immunoassay, if available (for cut-off point for antibody concentration see leaflet of the test kit employed). Depending on the outcome the physician will make appropriate recommendations. A confirmatory neutralization test may be performed so as to eliminate any risk of false positive enzyme immunoassay results due to cross-reactions as in the case of previous exposure to other flaviviridae such as yellow fever or dengue, including vaccination against these viruses.

In individuals with compromised immune status it is recommended that the specific antibody concentration be determined 2 years after completion of the primary vaccination course. If considered necessary, the booster injection may be given earlier.

Missed Dose

Extending the interval between the three doses of the primary vaccination schedule may leave subjects with inadequate protection against infection in the interim period.

Administration

Shake well prior to administration to thoroughly mix the vaccine suspension.

The vaccine is to be applied by intramuscular injection, preferably into the upper arm (deltoideus muscle). FSME-IMMUN must not be administered intravascularly. Intravascular administration may lead to severe hypersensitivity reactions.

For detailed instructions see the Patient Information Leaflet.

OVERDOSAGE

There is no experience of overdose. However, due to the presentation of the vaccine, accidental overdose in terms of volume is unlikely. If doses are administered closer together than recommended or more doses than requested are applied, undesirable effects may be expected.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Pharmacodynamics

The pharmacodynamic effect of the product consists of the induction of a sufficiently high concentration of anti-TBE antibody to provide protection against the TBE virus.

Special Populations and Conditions

Pediatrics:
This medical product is intended for persons over 16 years of age.

Geriatrics:
In individuals over 60 years of age the booster intervals should not exceed three years.

Duration of Effect

The seropositivity rates as determined by ELISA and NT three years after the third vaccination were 86.7 % and 94.2 %, respectively, suggesting that it is sufficient for the first booster to be administered three years after the completion of the primary vaccination series. Further investigations into the optimal timing of booster doses are ongoing.

The protection rate of the previous generation TBE vaccine has been determined during a continuous surveillance as performed among the total Austrian population since 1984. In this surveillance a protection rate of above 90% after the second vaccination and above 97% after completion of the primary vaccination schedule (3 doses) was calculated.

Based on a follow up surveillance performed among the total Austrian population for the years 2000 to 2006, a protection rate of 99 % was calculated with no statistically significant difference between age groups in regularly vaccinated persons. The protection rate in the first tick season, following 2 vaccinations was found to be at least as high as following completion of the primary vaccination schedule (three vaccinations) , but it is significantly lower in those with a record of irregular vaccination.

STORAGE AND STABILITY

FSME-IMMUN should be stored between +2°C to +8°C. FSME-IMMUN must not be used beyond the expiry date indicated on the package.

Freezing or storage at a higher temperature must be avoided, as the efficacy and tolerance of the vaccine may be impaired. Do not use if frozen even if for a short period of time. Store out of the reach and sight of children.

SPECIAL HANDLING INSTRUCTIONS

The vaccine should reach room temperature before administration. Shake well prior to administration to thoroughly mix the vaccine suspension. After shaking, FSME-IMMUN is an off-white, opalescent homogenous suspension. The vaccine should be inspected visually for any foreign particulate matter and/or variation in physical appearance prior to administration. In the event of either being observed, discard the vaccine.
Any unused product or waste material should be disposed of in accordance with local requirements.

Remove needle guard as follows:

1. Hold syringe at the lower part of the needle guard fixed onto the glass recipient.
2. Use the other hand to take the upper part of the needle guard between thumb and fore finger and twist to break the seal (tamper evident).
3. Remove the detached part of the needle guard from the needle by a vertical movement.

Following the removal of the needle guard FSME-IMMUN must be used immediately.

To avoid loss of sterility and/or clogging of the needle, it should not be left without protection for prolonged periods of time. Therefore, the needle guard should only be removed after shaking and immediately prior to use.

The administration of the vaccine should be documented by the physician, and the lot number recorded. A detachable documentation label is attached to each preloaded syringe.

DOSAGE FORMS, COMPOSITION AND PACKAGING

FSME-IMMUN is supplied in 0.5 ml single-dose, pre-filled disposable glass syringe (type I glass) with a plunger stopper (chlorobutyl isoprene rubber) and with needle attached for intramuscular injection. The container of this medicinal product contains latex rubber.

FSME-IMMUN is available in packs of 1 or 10.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	tick-Borne encephalitis virus vaccine, inactivated, with adjuvant
Chemical name:	tick-borne encephalitis vaccine, inactivated
Molecular formula and molecular mass:	not applicable
Structural formula:	not applicable
Physicochemical properties:	not applicable

Product Characteristics

FSME-IMMUN is a buffered solution of tick-borne encephalitis virus (strain Neudörfl) grown in cultures of chick embryo cells, inactivated with formaldehyde and adsorbed on aluminium hydroxide. It is a suspension for injection in a prefilled syringe.

Composition:

Each dose (0.5 mL) of the suspension for injection contains:

Active Substance: Tick-Borne Encephalitis Virus (strain Neudörfl)	2.4 micrograms
Adjuvant: Aluminum hydroxide, hydrated	0.35 milligram
Stabilizer: Human albumin	0.5 milligram
Buffer solution containing: Sodium chloride Disodium hydrogen phosphate dihydrate Potassium dihydrogen phosphate	 3.45 mg 0.22 milligrams 0.045 milligrams
Water for injection:	0.5 ml

Residues from the manufacturing process include sucrose, formaldehyde, protamine sulphate, neomycin and gentamicin.

Viral Inactivation

FSME-IMMUN is formaldehyde inactivated.

CLINICAL TRIALS

Study demographics and trial design

Table 2: Summary of patient demographics for clinical trials.

Study #	Study title	Dosage, route of administration and duration	Study subjects (n=number)	Age (Range)	Gender
201	Double-blind, randomized, dose-finding study to investigate the safety and immogenicity of two vaccinations with FSME-IMMUN in healthy volunteers ages 16 to 65 years	0.6 µg, 1.2µg, 2.4 µg, intramuscularly, two vaccinations approximately one month apart, duration approx. 13 weeks	411	16-65	Male and female
202	Open follow-up phase II study to investigate the safety and immunogenicity of a third vaccination with three antigen concentrations of FSME-IMMUN in healthy volunteers aged 16 to 65 years	0.6 µg, 1.2µg, 2.4 µg, intramuscularly third vaccination at approx. 6 months after first vaccination in Study 201, duration approx. 12 weeks	373	16-65	Male and female
208	Single-blind, randomized, multicenter comparison of FSME-IMMUN and ENCEPUR: safety and tolerability of two vaccinations in healthy volunteers aged 16 to 65 years	2.4 µg, intramuscularly, first and second vaccination approx. one month apart, duration approx 13 weeks	3999	16-65	Male and female
213	Open-label, mulitcenter, follow-up, phase III study to investigate the safety of the third vaccination of FSME-IMMUN in volunteers aged 16 to 66 years.	2.4 µg, intramuscularly, third vaccination approx. 6 months after the first vaccination in Study 208, duration approx. 16 weeks	3754	16-66	Male and female
223	Open-label follow-up study to investigate the seropersistence of TBE antibodies and the booster response to FSME-IMMUN in adults aged 18-67 years	2.4 µg, intramuscularly, 2 and 3 years follow-up after third vaccination in Study 213, duration approx. 13 months	347	18-67	Male and female
225	Open Phase IV Clinical Study to Evaluate the Immunogenicity and Safety of a Rapid Immunization Schedule with FSME-IMMUN in Healthy Adults aged 16-65 Years	2.4 µg, intramuscularly, first and second vaccination 12 ± 2 days apart, duration approx. 7 weeks	62	16-65	Male and female

690501	Open Label, Follow-up, Phase IV Clinical Study to Evaluate the Imunogenictiy and Safety of a Third Vaccination with FSME-IMMUN in Subjects Previously Vaccinated Using the Rapid Immunization Schedule	2.4 µg, intramuscularly, third vaccination approx. 12 months after the second vaccination in Study 225, duration approx. 4 weeks	44	16-65	Male and female
690601	Open label phase 3 B clinical study to evaluate the immunogenicity and safety of FSME-IMMUN with the first and second vaccination being administered according to a rapid immunization schedule in healthy adults aged 16 and older	2.4 µg, intramuscularly, first and second vaccination 12±2 days apart, third vaccination approx. 6 months after the first vaccination, duration approx. 8 months	348	16 - ≥ 50	Male and female

Study results

Table 3 Results of FSME-IMMUN studies
In clinical studies with FSME-IMMUN

- Seropositivity was defined as an ELISA value >126 VIE/Uml or NT titers ≥ 10.
- Seroconversion was defined if the ELISA value was < 63 VIE U/ml prior to study entry and > 126 VIE U/ml after the second/third vaccination and/or a negative neutralization test (< 1:10) at baseline and a titer of ≥ 1:10 after the second/third vaccination were obtained. Seroconversion in subjects with screening ELISA values between 63 and 126 VIE U/ml was defined as a more than 2-fold rise in antibody titers as compared to baseline after the second/third vaccination.

1. Results of FSME-IMMUN: Basic Immunization

<table>
<tr><th>Main Endpoints</th><th>Associated value and statistical significance for Drug at specific dosages</th></tr>
<tr><td>Study 201
Fever rate within 4 days after the first vaccination

Seroconversion rate within 21 days after the second vaccination as determined by ELISA and/or NT</td><td>
<table>
<tr><th>Dose</th><th>Probability of fever (%)</th><th>95 % C.I.</th></tr>
<tr><td>0.6 µg</td><td>0.0 %</td><td>0.0 % ; 2.7 %</td></tr>
<tr><td>1.2 µg</td><td>2.3 %</td><td>0.5 % ; 6.4 %</td></tr>
<tr><td>2.4 µg</td><td>0.0 %</td><td>0.0 % ; 2.8 %</td></tr>
</table>
<table>
<tr><th>Dose</th><th>Seroconversion rate (%)</th><th>95 % C.I.</th></tr>
<tr><td>0.6 µg</td><td>85.8 %</td><td>78.8 % ; 91.2 %</td></tr>
<tr><td>1.2 µg</td><td>96.9 %</td><td>92.4 % ; 99.2 %</td></tr>
<tr><td>2.4 µg</td><td>97.0 %</td><td>92.4 % ; 99.2 %</td></tr>
</table>
</td></tr>
</table>

Study 202

Local and systemic AEs within 4 days after the third vaccination

Dose	**Local reactions (%)**	**95 % C.I.**
0.6 µg	32.5 %	24.5 % ; 41.5 %
1.2 µg	25.8%	18.5 % ; 34.3 %
2.4 µg	36.4 %	27.8 % ; 45.8 %
Dose	**Systemic reactions (%)**	**95 % C.I.**
0.6 µg	11.1 %	6.2 % ; 17.9 %
1.2 µg	10.9 %	6.1 % ; 17.7 %
2.4 µg	10.2 %	5.4 % ; 17.1 %

Seroconversion rate within 21 days after the third vaccination as determined by ELISA and/or NT

Dose	**Seroconversion rate (%)**	**95 % C.I.**
0.6 µg	96.0 %	91.0 % ; 98.7 %
1.2 µg	99.2 %	95.7 % ; 100.0 %
2.4 µg	100.0 %	96.9 % ; 100.0 %

Study 208

Fever rate within 4 days after the first vaccination

Local and systemic reactions (excluding fever) within 21 days after the first and second vaccination

	Mild	**Moderate**	**Severe**
Fever (%)			
After 1 st vaccination	0.8 %	0.0 %	0.0 %
Local reactions (%)			
After 1 st vaccination	32.5 %	2.9 %	0.1 %
After 2 nd vaccination	28.3 %	3.2 %	0.2 %
Systemic reactions (%)			
After 1 st vaccination	11.7 %	1.9 %	0.0 %
After 2 nd vaccination	7.7 %	1.4 %	0.1%

Study 213

Local and systemic reactions within 4 days after the third vaccination

	%	**95 % C.I.**
Local reactions	29.7 %	28.0 % ; 31.5 %
Sytemic reactions	10.4 %	9.3 % ; 11.6 %

TBE antibody response within 35 days after the third vaccination as determined by ELISA and NT

Seroconversion rate	**ELISA (%)**	**95 % C.I.**	**NT (%)**	**95 % C.I.**
FSME-IMMUN [2]	98.8 %	97.2 % ; 99.6 %	98.8 %	97.2 % ; 99.6 %
Encepur/FSME-IMMUN"[3]	98.6%	95.2 % ; 99.8 %	98.6%	95.2 % ; 99.8 %

[2] Vaccination in study 208. In Study 213 all subjects received FSME-IMMUN for the third vaccination.
[3] Vaccination in study 208. In Study 213 all subjects received FSME-IMMUN for the third vaccination.

Study 223
Seropositivity rate measured by ELISA and NT at 2 and 3 years after the third vaccination in study 213 and within 35 days after the booster vaccination in this study.

Seropositivity rate	**ELISA (%)**	**95 % C.I.**	**NT (%)**	**95 % C.I.**
2 years after 3rd vaccination	84.1 %	79.0 % ; 88.4 %	96.0 %	92.8 % ; 98.1 %
3 years after 3rd vaccination	86.7 %	81.7 % ; 90.7 %	94.2 %	90.4 % ; 96.8 %
After booster vaccination	100.0 %	98.5 % ;100.0 %	100 %	98.5 % ;100.0 %

2. Results of FSME-IMMUN: Rapid Immunization Schedule

Study 225
Seropositivity rate after the second vaccination as determined by ELISA and NT

Seropositivity rate	**ELISA (%)**	**NT (%)**
Day 7 after 2nd vaccination	28.6 %	96.4 %
Day 14 after 2nd vaccination	92.9%	98.2 %
Day 21 after 2nd vaccination	96.4 %	100.0%

Study 690501
Seropositivity rate after the third vaccination as determined by ELISA and NT

Seropositivity rate	**ELISA (%)**	**NT (%)**
Days 7, 14 and 21 after 3rd vaccination	100%	100 %

Study 690601:
Seropositivity rate after the second and third vaccination as determined by ELISA and NT

Stratum A 16 – 49 years,

Seropositivity rate	**ELISA (%)**	**NT (%)**
Day 7 after 2nd vaccination	7.8 %	76.5 %
Day 14 after 2nd vaccination	73.9 %	94.8 %
Day 21 after 2nd vaccination	84.3 %	96.7 %
Day 7 after 3rd vaccination	87.6 %	97.2 %
Day 21 after 3rd vaccination	99.3 %	100.0 %

Stratum B ≥50 years

Seropositivity rate	**ELISA (%)**	**NT (%)**
Day 7 after 2nd vaccination	5.7 %	48.4 %
Day 14 after 2nd vaccination	48.4 %	80.9 %
Day 21 after 2nd vaccinatio□	69.6 %	88.0 □
Seropositivity rate	**ELISA (%)**	**NT (%)**
Day 7 after 3rd vaccination	6□.4 %	□4.3 %
Day 21 after 3rd vaccination	96.1 %	98.7 %

NT=Neutralization Test
ELISA=Enzyme Linked Immunoabsorbent Assay

DETAILED PHARMACOLOGY

Non-clinical trials

FSME-IMMUN with Human Serum Albumin and with Thiomersal.

Pharmacodynamics

Mice were mainly used for the pharmacodynamic investigations as the TBE virus causes the same disease in the laboratory mouse as in humans and the mouse is therefore a well-validated and suitable animal model to demonstrate potency of this vaccine.

Potency

Both the change in the manufacture of the active substance and the change in the pharmaceutical composition were evaluated using the mouse potency model. The tests were performed at release of each vaccine batch. For the potency tests stringent validity criteria are met on the basis of FSME-IMMUN.

Humoral Immunity

In addition to the potency and stability investigations as described above, the humoral immune response in mice receiving 0.2 ml of an undiluted vaccine, was evaluated using three different test methods (HAI test, neutralization test and TBE antibody ELISA).

With each of the three testing methods employed, the immunogenicity of the FSME-IMMUN (+human serum albumin +Thiomersal) candidate vaccine was found to be excellent, with marked seroconversion occurring in each of the experimental animals. The titer achieved after one single vaccination was high, in fact much higher than the protective titer (calculated from the mouse potency test). In addition, booster capacity was found to be good and significantly higher antibody levels were obtained after one booster injection than after single immunization.

Stability of Adjuvanted versus Non Adjuvanted Vaccine

In order to evaluate the stabilizing effect of aluminum hydroxide, results from potency tests obtained from three vaccine lots after one year storage were compared with values obtained with retention samples of non-adjuvanted vaccine lots (plain pool with human serum albumin). All three lots of the stored adjuvanted FSME-IMMUN (+human serum albumin +Thiomersal) candidate vaccine showed higher potency values than the non-adsorbed preparations. It can be concluded that the efficacy of the adsorbed FSME-IMMUN (+human serum albumin +Thiomersal) candidate vaccines at the end of its shelf life was significantly higher than the efficacy of the non-adsorbed preparation.

Anaphylaxis

In order to ascertain that the TBE candidate vaccine FSME-IMMUN (+human serum albumin +Thiomersal) did not contain additional anaphylactogenic substances from the CEC, a test for anaphylactic effects in guinea pigs was carried out. In this investigation the animals were immunized and boostered with CEC lysate to be subsequently challenged i.v. with 4 human doses of the TBE vaccine (non adjuvanted plain pool stabilized with human serum albumin).

The guinea pigs showed no anaphylactic reaction, neither immediately after intravenous challenge nor during the one-week observation period post-challenge. No alterations of organs were recorded. As a positive control, it was shown that CEC Iysate may induce anaphylaxis.

Pharmacokinetics

As described in the relevant CPMP Note for Guidance on Preclinical Pharmacological and Toxicological Testing of Vaccines (CPMP/SWP/465/95), pharmacokinetic studies (e. g. determining serum concentrations of antigens) are normally not needed. However, it states that local deposition studies would assess the retention at the site of injection and its further distribution and that histopathological studies of the draining lymph nodes (near the injection site) may illustrate deposit characteristics of the vaccine (see Safety).

Correlation Between Antibody Titer And Protection After Challenge

The mouse model was also used to correlate the antibody titer and the protection post-challenge. In this investigation the animals were immunized subcutaneously with different dilutions of the vaccine (starting with 1:9), the test was carried out in the same manner as in mouse potency testing.

After two subcutaneous immunizations, an immune response was detectable in all mice, using both neutralization test and ELISA (Holzmann et al. 1996).

The antibody titer was found to correlate with the vaccine dose applied, with higher titers generally being found in female mice. In the female mice, the PD_{50} as calculated from their survival rate was not found to differ significantly from PD_{50} as obtained from seroconversion. In the male mice, however, significant differences were noted, which were attributed to the stress experienced in male groups. A similar phenomenon was observed with the potency tests, where female animals have generally been observed to respond more homogenously. In summary, the evidence obtained showed a good correlation between dose of the vaccine and antibody titer for the female mice. PD_{50} as calculated on the basis of the seroconversion rate did not differ from PD_{50} based on survival rate. Male mice generally showed lower antibody titers after immunization. However, whereas the majority of male mice did not develop antibody titers assumed to be protective, the survival rate after challenge was similar to that of the female mice.

Safety

When manufacture of the active substance was changed, a preclinical safety study was conducted in guinea pigs. This study was carried out with the FSME-IMMUN (+human serum albumin +Thiomersal) vaccine prior to the initiation of clinical trials.

The purpose of the preclinical safety study was to investigate, on the one hand, whether injection of a two-fold human dose would induce changes at the injection site, and on the other hand, what the effects of the vaccine on the organs investigated are (liver, kidney, lung, brain, heart, spleen and the lymph nodes near the injection site).

At the injection site of treated animals, inflammation was observed up to 8 weeks post-injection, which was, however, found to completely disappear thereafter. The study demonstrated that there were no vaccine-induced changes in the lymph nodes, even though subcutaneous administration of 1 ml of an adjuvanted vaccine per animal at one site is a high dose, corresponding, in fact, to twice the dose given to humans intramuscularly.

From the data of this study, it was clearly demonstrated that the TBE candidate vaccine, FSME-IMMUN (+human serum albumin +Thiomersal), did not contain any toxic degradation products that would induce symptoms of stress in the animals (their weight was normal) or would lead to any changes in the organs investigated histologically. Nor were there any histopathological changes in the draining lymph nodes observed.

FSME-IMMUN with Human Serum Albumin and without Thiomersal

The long-standing history and widespread use of FSME-IMMUN together with the fact that safety and efficacy have been well established in the many years of application in the field, justify that no additional preclinical toxicity investigations were carried out with this vaccine after the removal of thiomersal from the formulation (Kunz et al. 1976).

No new single dose toxicity tests were carried out for the FSME-IMMUN (+human serum albumin –Thiomersal) vaccine, since it has not been possible to bind higher concentrations of the active substance (the virus antigen) to aluminum hydroxide in the presence of human serum albumin. This decision was also taken in consideration of animal welfare and Austrian law, as animal experiments are prohibited if they are not expected to yield new information.

In addition, it is worth noting that FSME-IMMUN without thiomersal has been shown to be equivalent to FSME-IMMUN with thiomersal in terms of safety and immunogenicity in a clinical study in 1191 adults (see Clinical Trials; Barrett et al. 2003).

TOXICOLOGY

Single Dose Toxicity

Since none of the toxicity studies with FSME-IMMUN (+human serum albumin +Thiomersal) demonstrated any harmful effects in the experimental animals, and since, in the presence of human serum albumin, it had not been possible to bind higher concentrations of the active substance (the virus antigen) to aluminum hydroxide, no new single dose toxicity tests were carried out for the FSME-IMMUN (+human serum albumin -Thiomersal) vaccine. This decision was also taken in consideration of animal welfare and protection.

In addition, it is worth repeating that in the safety study described earlier, no harmful events had been noted.

Local Tolerance After Subcutaneous Administration

As described earlier, local tolerance of FSME-IMMUN had been found to be satisfactory and this was corroborated for the candidate vaccine in a study in guinea pigs, where injection was frequently followed by granuloma formation, but there was no significant difference between animals receiving a human dose of FSME-IMMUN (+human serum albumin + Thiomersal) candidate vaccine subcutaneously and the control group that received adjuvanted buffer subcutaneously.

Local Tolerance After Intradermal Administration

In addition to the above-mentioned local tolerance investigation after subcutaneous injection of FSME-IMMUN (+human serum albumin +Thiomersal) candidate vaccine, a second study of local tolerance following intradermal injection of the FSME-IMMUN (+human serum albumin +Thiomersal) candidate vaccine was carried out in guinea pigs. The following amounts were injected into the shaved backs of the guinea pigs: 100:l of the concentrated vaccine and also 100:l of 1:3 and 1:10 diluted vaccine.

Intradermal injection of FSME-IMMUN (+human serum albumin +Thiomersal) into guinea pigs caused a harmless acute skin reaction of a temporary nature (e. g. slight redness, swelling, increased blood supply) as did adjuvanted buffer. A severe skin reaction, such as insufficient blood supply or necrosis, was not observed in any of the animals.

In addition to the studies described above, pyrogen testing is performed at different manufacturing stages in the course of quality control. Production sterility testing is carried out at each stage of manufacture and the purity of the active substance is demonstrated using gradient centrifugation.

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PART III: CONSUMER INFORMATION
FSME-IMMUN
Tick-Borne Encephalitis Virus Vaccine, Inactivate, with Adjuvant

This leaflet is part III of a three-part "Product Monograph" published when FSME-IMMUN was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about FSME-IMMUN. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS VACCINE

What the vaccine is used for:

FSME-IMMUN is a vaccine, which is used to prevent disease caused by Tick-Borne Encephalitis (TBE) Virus. It is suitable for persons of at least 16 years of age.

The Tick-Borne Encephalitis Virus can cause very serious infections of the brain or the spine and its covering. These often start with headache and high temperature. In some people and in the most severe forms, they can progress to loss of consciousness, coma and death.

The virus can be carried by ticks. It is passed on to man by tick bites. The chance of being bitten by ticks that carry the virus is high in some parts of central and northern Europe. People who live in or take holidays in these parts of Europe are most at risk. The ticks are not always spotted on the skin and the bites may not be noticed.

- Like all vaccines, FSME-IMMUN may not completely protect everyone who is vaccinated.
- Also, protection does not last for life.
- A single dose of the vaccine is not likely to protect you against infection. You need 3 doses (please refer to the vaccination schedule for more information).

What it does:

FSME-IMMUN provides protection against tick-borne encephalitis and should be given before the start of the tick activity season. The season begins in the spring and so your course of vaccination should preferably start in the winter months.

The vaccine works by causing the body to make its own antibodies, which protect against this disease.

Please note: A tick bite may also cause infection with Borrelia bacteria. The symptoms of such infections may resemble those of tick-borne encephalitis. TBE vaccines like FSME-IMMUN do not provide protection against Borrelia infections.

As with all vaccines, FSME-IMMUN may not completely protect all patients receiving the vaccine against the infection that it is intended to prevent.

When it should not be used:

Do not use FSME-IMMUN if:

- you ever had an allergic reaction to a previous dose of this vaccine or to any ingredient of the vaccine. For example, you have had skin rash, swelling of the face and throat, difficulty in breathing, blue discoloring of the tongue or lips, low blood pressure and collapse.
- you ever had an allergic reaction to neomycin or gentamicin or to formaldehyde or protamine sulphate (used during the manufacturing process).
- you ever had cross-allergies with aminoglycosides
- you ever had a severe allergic reaction after eating egg or chicken.
- you are known to be allergic to latex rubber.
- you have an infection with a fever (raised temperature) you may have to wait before having FSME-IMMUN. Your doctor could ask you to wait for the injection until you feel better.

What the medicinal ingredient is:

Tick-borne Encephalitis Virus Vaccine, Inactivated, with Adjuvant

What the important nonmedicinal ingredients are:

2% Aluminum hydroxide suspension, disodium hydrogen phosphate dehydrate, 0.1% human albumin, potassium dihydrogen phosphate, sodium chloride, water for injection.

Residues of formaldehyde, gentamicin, sucrose, neomycin, and protamine sulphate may be present.

For a full listing of nonmedicinal ingredients see Part 1 of the product monograph.

What dosage forms it comes in:

Each dose contains 2.4 micrograms (target value) inactivated tick-borne encephalitis virus.

The vaccine is provided in a one-dose (0.5 mL) prefilled glass syringe for use in individuals aged 16 years and above.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Talk to your doctor before having the vaccine if you

- are allergic (hypersensitive) to the active substance, any of the other ingredients or neomycin, gentamycin, formaldehyde or protamine sulphate (used during the manufacturing process)
- ever had a severe allergic reaction after eating egg or chicken
- are known to be allergic to latex rubber
- have an autoimmune disease (such as rheumatoid arthritis or multiple sclerosis)
- have a weak immune system (so that you do not fight infections well)
- do not produce antibodies well
- take any medicine for cancer
- take medicines called corticosteroids (that reduce inflammation)
- have any brain illness (such as demyelinating disorders or poorly controlled epilepsy)

Vaccination should be postponed in patients with acute clinical conditions (with or without fever) that could be aggravated by adverse reactions to the vaccine or could impair the interpretation of possible adverse reactions to the vaccine.

INTERACTIONS WITH THIS VACCINE

Drugs that may interact with FSME-IMMUN include:
No interaction studies with other vaccines or medicinal products have been performed. The administration of other vaccines at the same time as FSME-IMMUN should be performed only in accordance with official recommendations. If other injectable vaccines are to be given at the same time, administrations should be into separate sites and, preferably, into separate limbs.

A protective immune response may not be elicited in persons undergoing immunosuppressive therapy or persons with an impaired immune system (for vaccination schedule please see section "proper use of this vaccines"). There are no specific clinical data on which to base dose recommendations in such patients.

PROPER USE OF THIS VACCINE

Usual dose:
Recommended dosage for FSME-IMMUN (tick-borne encephalitis virus vaccine, inactivated, with adjuvant) is summarized in the following table:

VACCINATION SCHEDULE

Basic Immunization	Dose	Interval
1st dose	0.5 mL i.m.	-
2nd dose	0.5 mL i.m.	1 to 3 months after the 1st vaccination
3rd dose	0.5 mL i.m.	5 to 12 months after the 2nd vaccination

Rapid Immunization Schedule	Dose	Interval
1st dose	0.5 mL i.m.	-
2nd dose	0.5 mL i.m.	2 weeks after the 1st vaccination
3rd dose	0.5 mL i.m.	5 to 12 months after the 2nd vaccination

The doctor or nurse will inject the recommended dose of the vaccine.

FSME-IMMUN will be injected into the deltoid muscle of your upper arm. Intravascular administration may lead to severe hypersensitivity reactions. A complete vaccination course involves 3 doses of the vaccine. The second dose will be given between 1 to 3 months after the first dose and the third dose will be given 5 to 12 months after the second dose. A booster vaccination is then necessary every 3 to 5 years.
In order to quickly achieve protection, as may for instance be necessary when the first dose is given in the summer months, the second dose may be given 14 days after the first injection.

It is important to follow the instruction from the doctor/nurse regarding return visits for the follow-up doses.

Overdose:

An overdose is highly unlikely to happen because the injection is given from a single-dose syringe by a doctor.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

If you have any further questions on the use of this vaccine, ask your doctor or pharmacist.

Missed Dose:

If you leave too much time between the 3 doses, you may not have full protection against infection.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

As with all medicines, FSME-IMMUN may cause side effects in some persons. If any side effects worry you, or you have any unusual symptoms, please contact your doctor. As with all vaccines, severe allergic reactions can happen. They are very rare, but the right medical treatment and supervision must always be readily available. Symptoms of serious allergic reactions include:

- swelling of the lips, mouth, throat (which may make it difficult to swallow or breathe),
- a rash and swelling of the hands, feet and ankles,
- loss of consciousness due to a drop in blood pressure.

These signs or symptoms usually happen very quickly after the injection is given, while the person is still in the clinic. If any of these symptoms happen after you leave the place where your injection was given, you must see a doctor IMMEDIATELY.

The following side effects have been reported in clinical safety studies

Very common side effects
Pain, where the injection was given

Common side effects
Headache, nausea, feeling tired or unwell, muscle and joint pains

Uncommon side effects
Swelling of lymph glands, vomiting, fever, injection site hemorrhage

Rare side effects
Allergic reactions, sleepiness or drowsiness, diarrhea, abdominal pain, dizziness characterized by a sensation of whirling motion, injection site induration, injection site swelling, injection site paresthesia, injection site warmth, injection site erythema, injection site itching

The following additional side effects have been reported under the spontaneous reporting system

- Rapid beating of the heart
- Blurred vision or being more sensitive to light, pain in the eye
- Chills, weakness, influenza-like illness, unsteady walking, local swelling
- Severe allergic (anaphylactic) reaction, and aggravation of autoimmune disease (e.g., Multiple sclerosis)
- Neck pain, muscle stiffness, pain in arms and/or legs
- Ringing in the ears (tinnitus)
- Shortness of breath
- Signs of meningeal irritation like stiffness of neck, feeling dizzy, inflamed nerves of various degrees (e.g., abnormal or reduced sensation, facial nerve paralysis, paresis), convulsion, inflammation of the brain (encephalitis)
- Damage of the myelin sheath, the material that surrounds and protects your nerve cells (demyelination)
- Rashy and/or itchy skin, hives, redness of skin, inflammation of skin, sweating
- Herpes zoster (triggered in pre-exposed patients)

If you notice any other side effects not mentioned in this leaflet, please inform your doctor or pharmacist (chemist).
This is not a complete list of side effects. For any unexpected effects while taking FSME-IMMUN, contact your doctor or pharmacist.

REPORTING SUSPECTED SIDE EFFECTS

To monitor vaccine safety, the Public Health Agency of Canada collects information on serious and unexpected adverse events following vaccination. If you suspect you have had a serious or unexpected event following receipt of a vaccine you may notify the Public Health Agency of Canada:

By toll-free telephone: 866-844-0018
By toll-free fax: 866-844-5931
Email: cacfi@phac-aspc.gc.ca
Web: http://www.phac-aspc.gc.ca/im/vs-sv/index-eng.php

Mail:
The Public Health Agency of Canada
Vaccine Safety Section
130 Colonnade Road
Ottawa, Ontario K1A 0K9
A/L: 6502A

NOTE: Should you require information related to the management of side effect, please contact your health care provider before notifying the Public Health Agency of Canada. The Public Health Agency of Canada does not provide medical advice.

HOW TO STORE IT

Store your vaccine in a refrigerator between +2°C to +8°C. The vaccine should not be frozen, not even for a short period of time.

Store the vaccine out of the reach of children.

The expiry date is indicated on the label and packaging. The vaccine should not be administered after this date.

Following use, the syringe is disposed of in accordance with the relevant national regulations.

Specific information for the health care provider

Shake well prior to administration to thoroughly mix the vaccine suspension.
Remove needle guard as follows:

1. Hold the syringe at the lower part of the needle guard fixed onto the glass recipient (fig. 1);
2. Use the other hand to take the upper part of the needle guard between thumb and forefinger, and twist to break the seal (fig. 2).
3. Remove the detached part of the needle guard from the needle by a vertical movement (fig. 3).

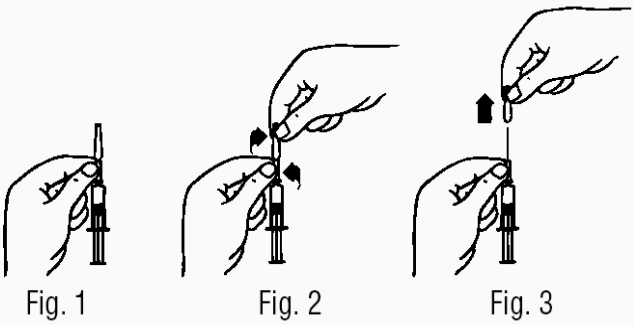

Fig. 1 Fig. 2 Fig. 3

Following twisting-off and removal of the needle guard, FSME-IMMUN can be used immediately. To avoid loss of sterility and/or clogging of the needle, it should not be left without protection over prolonged periods of time. Therefore, the needle guard should only be removed immediately before use.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.baxter.com
or by contacting the sponsor, Baxter Corporation,
at: 1-800-387-8399

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