Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

TicoVac 0.5 ml Suspension for injection in a pre-filled syringeTick-Borne Encephalitis Vaccine (whole Virus, inactivated)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose (0.5 ml) 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)

Excipient(s) with known effect
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Suspension for injection in a pre-filled syringe
After shaking the vaccine is an off-white, opalescent suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

TicoVac 0.5 ml is indicated for the active (prophylactic) immunization of persons of 16 years of age and older against tick-borne encephalitis (TBE).

TicoVac 0.5 ml is to be given on the basis of official recommendations regarding the need for, and timing of, vaccination against TBE.

4.2 Posology and method of administration

Posology

Primary vaccination schedule
The primary vaccination schedule is the same for all persons from the age of 16 onwards and consists of three doses of TicoVac 0.5 ml.
The first and second dose should be given at a 1 to 3 month interval.
If there is a need to achieve an immune response rapidly, the second dose may be given two weeks after the first dose.
After the first two doses sufficient protection for the ongoing tick season is to be expected (see section 5.1).

The third dose should be given 5 to 12 months after the second vaccination. After the third dose protection is expected to last for at least 3 years. 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.

Basic Immunization	**Dose**	**Conventional Schedule**	**Rapid Immunization Schedule**
1st dose	0.5 ml	Elected date	Elected date
2nd dose	0.5 ml	1 to 3 months after the 1st vaccination	14 days after the 1st vaccination
3rd dose	0.5 ml	5 to 12 months after the 2nd vaccination	5 to 12 months after the 2nd vaccination

Booster doses
Persons from 16 to 60 years of age
The first booster dose should be given 3 years after the third dose (see section 5.1). Sequential booster doses should be given every 5 years after the last booster dose.

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

Booster dose ≥ 16 to < 60 years	**Dose**	**Timing**
1stbooster	0.5 ml	3 years after the 3rd vaccination
Sequential booster doses	0.5 ml	every 5 years

Booster dose ≥ 60 years	**Dose**	**Timing**
All booster doses	0.5 ml	every 3 years

Extending the interval between any of the doses (primary vaccination schedule and booster doses) may leave subjects with inadequate protection against infection (see section 5.1).
However, in the case of an interrupted vaccination schedule of at least two previous vaccinations, a single catch-up dose is sufficient to continue the vaccination schedule (see section 5.1).

Persons with impaired immune system (including those undergoing immunosuppressive therapy)
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. The same applies to any of the following doses.

Method of administration

The vaccine should be given by intramuscular injection into the upper arm (deltoid muscle).

In exceptional cases only (in subjects with a bleeding disorder or in subjects receiving prophylactic anticoagulation), the vaccine may be administered subcutaneously (see sections 4.4 and 4.8).

Care must be taken to avoid accidental intravascular administration (see section 4.4).

4.3 Contraindications

Hypersensitivity to the active substance, any of the excipients listed in section 6.1, or production residues (formaldehyde, neomycin, gentamycin, protamine sulfate). Cross allergies with aminoglycosides other than neomycin and gentamycin should be considered.

Severe hypersensitivity to egg and chick proteins (anaphylactic reaction after oral ingestion of egg protein) may cause severe allergic reactions in sensitized individuals (see also section 4.4).
TBE vaccination should be postponed if the person is suffering from a moderate or severe acute illness (with or without fever).

4.4 Special warnings and precautions for use

As with all vaccines that are administered by injection, appropriate emergency treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine.

Non-severe allergy to egg protein does not usually constitute a contraindication to vaccination with TicoVac 0.5 ml. 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”.

Intravascular administration must be avoided as this might lead to severe reactions, including hypersensitivity reactions with shock.

The recommended route of administration is intramuscular. However, this may not be appropriate in subjects with a bleeding disorder or subjects receiving prophylactic anticoagulation. Limited data in healthy adults suggest comparable immune response for subcutaneous booster vaccinations when compared to intramuscular booster vaccinations. However, subcutaneous administration might lead to an

increased risk for local adverse reactions. No data are available for the elderly. Furthermore, no data are available for primary immunization via the subcutaneous route.

A protective immune response may not be elicited in persons undergoing immunosuppressive therapy.
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.

In case of a known or suspected auto-immune disease in the intended recipient, the risk of TBE infection must be weighed against the risk that TicoVac 0.5 ml might have an adverse effect on the course of the auto-immune disease.

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.

There is no data concerning post exposure prophylaxis with TicoVac 0.5 ml.
As with all vaccines, TicoVac 0.5 ml may not completely protect all vaccinees against the infection that it is intended to prevent. For details on product administration in the elderly and persons with impaired immune system please see section 4.2.

Tick bites may transmit infections other than TBE, including certain pathogens that can sometimes cause a clinical picture that resembles tick-borne encephalitis. TBE vaccines do not provide protection against Borrelia infection. Therefore, the appearance of clinical signs and symptoms of possible TBE infection in a vaccinee should be thoroughly investigated for the possibility of alternative causes.

4.5 Interaction with other medicinal products and other forms of interactions

No interaction studies with other vaccines or medicinal products have been performed. The administration of other vaccines at the same time as TicoVac 0.5 ml 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.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data from the use of TicoVac 0.5 ml in pregnant women.

Breast-feeding

It is unknown whether TicoVac 0.5 ml is excreted in human milk.
Therefore, TicoVac 0.5 ml should only be administered during pregnancy and to breastfeeding women when it is considered urgent to achieve protection against TBE infection and after careful consideration of the risk-benefit relationship.

4.7 Effects on ability to drive and use machines

TicoVac 0.5 ml 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.

4.8 Undesirable effects

The frequencies provided in the table below are per vaccination and have been calculated based on a pooled analysis of adverse reactions from 7 clinical studies conducted with TicoVac 0.5 mL (2.4 µg) in subjects aged 16 through 65 years receiving 3 vaccinations (3512 subjects after the first vaccination, 3477 after the second vaccination, and 3274 after the third vaccination).
The ADRs listed in this section are given according to the recommended frequency convention:

Adverse Reactions from clinical trials

System organ class	**Frequency**			
	Very common (≥1/10)	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**
Blood and lymphatic system disorders			Lymphadenopathy	
Immune system disorders				Hypersensitivity
Nervous system disorders		Headache		Somnolence
Ear and labyrinth disorders				Vertigo[1]
Gastrointestinal disorders		Nausea	Vomiting	Diarrhoea Abdominal pain
Musculoskeletal and connective tissue disorders		Myalgia Arthralgia		
General disorders and administration site conditions	Injection site reactions e.g., Injection site pain	Fatigue Malaise	Pyrexia Injection site hemorrhage	Injection site reactions such as · Erythema · Induration · Swelling · Pruritus · Paraesthesia · Warmth

[1] The frequency of vertigo is based on the rate reported after the first vaccination (n=3512). Vertigo was not reported after the second or third vaccinations.

Adverse reactions from post-marketing surveillance

The following additional adverse reactions have been reported in post-marketing experience.

System organ class	Frequency*
	Rare (≥1/10,000 to <1/1,000)
Infections and infestations	Herpes zoster (triggered in pre-exposed patients)
Immune system disorders	Precipitation or aggravation of autoimmune disorders (e.g. multiple sclerosis), anaphylactic reaction
Nervous system disorders	Demyelinating disorders (acute disseminated encephalomyelitis, guillain-barré syndrome, myelitis, transverse myelitis), encephalitis, convulsions, aseptic meningitis, meningism, sensory abnormalities and motor dysfunction (facial palsy/paresis, paralysis/paresis, neuritis, hypoesthesia, paresthesia), neuralgia, optic neuritis, dizziness
Eye disorders	Visual impairment, photophobia, eye pain
Ear and labyrinth disorders	Tinnitus
Cardiac disorders	Tachycardia
Respiratory, thoracic and mediastinal disorders	Dyspnea
Skin and subcutaneous tissue disorders	Urticaria, rash (erythematous, maculopapular), pruritus, dermatitis, erythema, hyperhidrosis
Musculoskeletal and connective tissue disorders	Back pain, joint swelling, neck pain, musculoskeletal stiffness (including neck stiffness), pain in extremity
General disorders and administration site conditions	Gait disturbance, chills, influenza-like illness, asthenia, edema, injection site joint movement impairment such as joint pain, nodule and inflammation

* The upper limit of the 95% confidence interval of the event frequency is calculated with 3/n, with n representing the number of subjects included in all clinical trials with TicoVac0.5 ml. Therefore, the calculated frequency "rare" represents the theoretical maximum frequency for these events

In a small comparative study on the immune response after intramuscular and subcutaneous administration of FSME-IMMUN in healthy adults, the subcutaneous route led to a higher local reactogenicity profile, particularly in women.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie

4.9 Overdose

No case of overdose has been reported. However, due to the presentation of the vaccine, accidental overdose in terms of volume is unlikely.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: encephalitis vaccines, ATC Code: J07 BA01

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.

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 is at least as high after the first two vaccinations, following the conventional and rapid vaccination, i.e before completion of the basic vaccination scheme by the third vaccination. In those with a record of irregular vaccination the protection rate is significantly lower.
In clinical studies with TicoVac 0.5 ml, seropositivity was defined as an ELISA value > 126 VIE U/ml or NT titers ≥10. Pooled seropositivity rates determined by ELISA and NT at 21 days after the second and third vaccinations in the conventional and the rapid immunization schedule are presented in table 1 and 2.

Table 1.
Conventional immunization schedule, pooled seropositivity rates [1] as determined by ELISA and NT in subjects aged 16-65 years

	ELISA[2]		**NT[2]**	
Dose	2nd	3rd	2nd	3rd
Seropositivity rate[1],% (n/N)	87.5 (420/480)	98.7 (825/836)	94.8 (330/348)	99.4 (714/718)

Table 2.
Rapid immunization schedule, pooled seropositivity rates [1] as determined by ELISA and NT

	ELISA[2]		**NT[2]**	
Dose	2nd	3rd	2nd	3rd
Seropositivity rate of subjects aged 16-49 years, % (n/N)	86.6 (168/194)	99.4 (176/177)	97.4 (189/194)	100.0 (177/177)
Seropositivity rate of subjects aged ≥ 50 years, % (n/N)	72.3 (125/173)	96.3 (155/161)	89.0 (154/173)	98.8 (159/161)

[1] – evaluated 21 days after each dose
[2] - Seropositivity cut-off: ELISA >126 VIE U/ml; NT ≥ 1:10

The highest seropositivity rates as determined by ELISA and NT in both age groups were achieved upon administration of the third dose. Therefore, completion of the primary vaccination schedule of three doses is necessary to achieve protective antibody levels in almost all recipients.

Rapid immunization with TicoVac 0.5 ml resulted in high seropositivity rates determined by NT as early as 14 days after the second vaccination (89.3%) and 7 days after the third vaccination (91.7%).

Results from a follow-up study that investigated the persistence of TBE antibodies support the need for the first booster vaccination no later than three years after primary immunization. In adults aged up to 50 years seropositivity rates determined by NT remained high until 5 years after the first booster vaccination (94.3%); only slightly lower rates (> 90.2%) were observed in subjects aged 50 -60 years supporting a 5-year booster interval from the first booster onwards for subjects below 60 years of age.

TicoVac vaccination induces statistically equivalent titers of TBE virus neutralizing antibodies against European, Siberian and Far Eastern TBE virus strains. In a published clinical study considerable cross-neutralizing antibodies were also induced against Omsk Hemorrhagic Fever Virus, however titers were lower than against the TBE virus subtypes.
A study on the persistence of immune memory in individuals from the age of 6 years and older whose vaccination intervals were longer than recommended was performed. In individuals that have received at least one primary dose in the past, a single catch-up vaccination with FSME-IMMUN 0.5 ml was able to elicit an anamnestic antibody response as measured by ELISA in 99% of adults ≥16 - <60 years and in 96% of adults ≥60 years, irrespective of the time elapsed since the last vaccination (≤ 20 years). No data are available on antibody response as measured by NT.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Human albumin
Sodium chloride
Disodium phosphate-dihydrate
Potassium dihydrogenphosphate
Water for injections
Sucrose
Aluminium hydroxide, hydrated.

6.2 Incompatibilities

In the absence of compatibility studies, this vaccine must not be mixed with other medicinal products.

6.3 Shelf life

30 months.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Keep the syringe in the outer carton in order to protect from light. Do not freeze.

6.5 Nature and contents of container

0.5 ml of suspension in pre-filled syringe (type I glass) with a plunger stopper (halogenobutyl rubber), without needle attached. Pack sizes of 1, 10, 20 and 100. The pack may include 0 needles or 1 needle. Needles are sterile and for single use only. Not all pack sizes may be marketed.

Each pre-filled syringe is packed in a blister. The opening in the blister seal is intended and allows for the equilibration of moisture during the recommended warm-up prior to the administration of the vaccine. Open the blister by removing the lid to take out the syringe. Do not press the syringe through the blister.

For subcutaneous administration, see section 6.6.

6.6 Special precautions for disposal and other handling

The vaccine should reach room temperature before administration. Shake well prior to administration to thoroughly mix the vaccine suspension. After shaking, TicoVac 0.5 ml 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.

After removing the syringe cap, attach the needle immediately and remove the needle shield prior to administration. Once the needle is attached, the vaccine must be administered immediately. In the exceptional cases of subcutaneous administration, an appropriate needle should be used.

Any unused product or waste material should be disposed of in accordance with local requirements.

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.

7 MARKETING AUTHORISATION HOLDER

Pfizer Healthcare Ireland
9 Riverwalk
National Digital Park
Citywest Business Campus
Dublin 24

8 MARKETING AUTHORISATION NUMBER

PA0822/184/001

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10 DATE OF REVISION OF THE TEXT

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