



HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

28 April 2010

ENCEPUR 1.5 µg / 0.5 ml, suspension for injection in prefilled syringe. Tick-borne encephalitis vaccine (inactivated, adsorbed).
B/1 glass prefilled syringe containing 0.5 ml with needle (CIP: 367 745-3)

Applicant: NOVARTIS VACCINES AND DIAGNOSTICS

Tick-borne encephalitis vaccine, strain K23

ATC code (2010): J07BA01

Date of Marketing Authorisation: 4 August 2005 (national procedure)

Reason for request: Inclusion on the list of medicines approved for use by hospitals.

Additional documents

Opinion of the Haut Conseil de la santé publique [High Council for Public Health] dated 23 October 2009 on the use of Encepur® in preventing central European tick-borne encephalitis:

http://www.hcsp.fr/docspdf/avisrapports/hcspa20091023_encephatiquence.pdf

Opinion of the Haut Conseil de la santé publique dated 11 December 2009 on the minimum information requirements for publicity material relating to the tick-borne encephalitis vaccine Encepur :

http://www.hcsp.fr/docspdf/avisrapports/hcspa20091211_encephatiquence.pdf

Vaccination timetable and recommendations for 2010 according to the opinion of the Haut Conseil de la santé publique. BEH [weekly epidemiological bulletin], 22 April 2010, n°14-15

http://www.invs.sante.fr/beh/2010/14_15/beh_14_15.pdf

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Tick-borne encephalitis virus, strain K23

Adsorbed on hydrated aluminium hydroxide.

Produced on chicken embryonic fibroblast cells (CEF cells).

1.2. Indication

“ENCEPUR is indicated for active (prophylactic) immunisation against tick-borne encephalitis in adults and children aged 12 or over.

ENCEPUR should be administered according to the official guidelines defining requirements and to the vaccination schedule for tick-borne encephalitis.”

1.3. Dosage

“The primary vaccination schedule for adults and children aged 12 or over consists of 3 injections of ENCEPUR.

The first injection must be given on a fixed date and the second must be given 1 to 3 months later. The third injection must be given 9 to 12 months after the second one.

If a rapid immunological response is needed, the three injections may be given according to an accelerated timetable: the first dose on D0, the second seven days later (D7) and the third 21 days after the initial dose (D21).

Seroconversion is usually certain no sooner than 14 days after the second injection.

If the intervals between the three injections are exceeded, subjects may be inadequately protected against infection during these intervals.

Booster doses for exposed subjects

This first booster dose must be given within three years of injection of the third dose.

Where primary vaccination has been carried out according to the accelerated vaccination schedule, the first booster dose must be given 12 to 18 months after primary vaccination.

Booster doses may be given every 3 to 5 years if the subject remains exposed to risk of infection.

Immunodeficient subjects and subjects aged 60 or over

There is insufficient clinical data to allow a vaccination schedule to be defined for this population.

However, levels of specific antibodies can be measured four weeks after the second injection according to the conventional schedule. An additional injection can be given if seroconversion has not taken place. The third and final injection must be given according to the vaccination schedule which has been determined.

Levels of specific antibodies can be measured four weeks after the third dose in the case of subjects receiving vaccinations according to the accelerated timetable. An additional injection can be given if seroconversion has not taken place.

The need for booster doses should be assessed according to the results of specific antibody tests performed at regular intervals. In general, the interval between booster doses for subjects aged 60 and over should not exceed three years.”

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification

J : Anti-infectives for systemic use
J07 : vaccines
J07B : viral vaccines
J07BA : encephalitis vaccines
J07BA01 : encephalitis, tick borne, inactivated, whole virus.

2.2. Medicines in the same therapeutic category

2.2.1 Strictly comparable medicines

NN	Trade name	indication	Status
Tick-borne encephalitis virus, inactivated neudoerfl strain	TICOVAC 0.5 ml ADULTES, suspension for injection in prefilled syringe.	TICOVAC 0.5 ml ADULTES is indicated for active (prophylactic) immunisation against tick-borne encephalitis in subjects aged 16 or over.	Approved for use by hospitals
Tick-borne encephalitis virus, inactivated neudoerfl strain	TICOVAC 0.25 ml ENFANTS, suspension for injection in prefilled syringe.	TICOVAC 0.25 ml ENFANTS is indicated for active (prophylactic) immunisation against tick-borne encephalitis in children over one and under 16.	Approved for use by hospitals

2.3. Medicines in the same therapeutic category

Not applicable

3. ANALYSIS OF AVAILABLE DATA

The company submitted three clinical studies (V48P1, V48P2, V48P5) carried out in adults and adolescents aged 12 and over comparing the current formula of ENCEPUR (which does not contain polygeline or human albumin) with the previous formula, which was withdrawn from the market because of the frequency of allergic reactions. This previous formula was placed on the market in Germany in 1991 but was never sold in France.

Three studies including children aged 1 to 11 were not taken into consideration as this population does not match the marketing authorisation.

A publication describing a clinical study which compared the old formula of ENCEPUR (containing polygeline) with another vaccine for tick-borne encephalitis was not taken into consideration as that formula is not the one currently being assessed.

3.1. Efficacy

3.1.1 Study V48P1

Method

Randomised, single-blind study with two parallel groups comparing the old and new formulas of the vaccine ENCEPUR in healthy adult volunteers aged between 18 and 40.

The injections were given on D0, D7 and D21.

Assessment endpoints: immunogenicity three weeks after the end of vaccination (at D42 ± 3 days)

- Primary endpoint: level of antibodies measured by a neutralisation test (internal test: Chiron-Behring);

- Secondary endpoints: level of antibodies measured by a neutralisation test (Holzmann test) and two ELISA tests (internal tests, Chiron-Behring and Enzygnost).

Descriptive statistical analysis.

Results

A total of 44 subjects were included (22 per group), four of whom (two in each group) were excluded from analysis because of “major protocol deviations” (two local corticosteroid treatments and two antihypertensive treatments).

The immunogenicity results are shown in *table 1*

Table 1: antibody titres

Test	Vaccine (n=20/group)	Geometric mean on D42 (95%CI)	Ratio of geometric means D42/D0 (95%CI)
Neutralisation (internal)	New formula	308 (241-393)	279 (215-361)
	Old formula	425 (333-543)	405 (313-525)
Neutralisation (Holzmann)	New formula	9.33 (7.62-11)	1.87 (1.52-2.28)
	Old formula	10 (8.17-12)	2 (1.63-2.45)
ELISA (Enzygnost)	New formula	17(13-22)	6.4 (4.96-8.25)
	Old formula	29 (22-38)	11 (8.62-14)
ELISA (internal)	New formula	3.36 (2.48-4.56)	3.9 (2.77-5.48)
	Old formula	5.67 (4.18-7.69)	7.54 (5.36-11)

CI = confidence interval

The seroconversion threshold for the Holzmann neutralisation test was a titre of ≥ 10 . No seroconversion threshold was defined for the other tests.

The seroconversion rate on D42 is shown in *table 2*.

Table 2: seroconversion rate*

Vaccine (n=20/group)	seroconversion rate (95%CI)
New formula	75% (51%-91%)
Old formula	80% (56%-94%)

*antibody titre ≥ 10 with the Holzmann neutralisation test;

CI = confidence interval

3.1.2 Study V48P2

Method

Randomised, double-blind study with two parallel groups comparing the old and new formulas of the vaccine ENCEPUR in healthy adult volunteers aged between 18 and 40.

The injections were given on D0, D7 and D21.

Primary objective : to demonstrate the non-inferiority of the new formula compared to the old formula for the antibody level measured by a neutralisation test (internal test: Chiron-Behring), 3 weeks after the end of vaccination (at D42 \pm 3 days);

Secondary objectives:

- To investigate the kinetics of the immune response up to 35 days after the 3rd vaccination, assessed by a neutralisation test (internal Chiron-Behring test and Holzmann test) and an ELISA test (Enzygnost);
- To investigate the level of antibodies measured by an ELISA test (Enzygnost) 3 weeks after the end of vaccination;
- To investigate the level of antibodies measured by a neutralisation test (Holzmann) 3 weeks after the end of vaccination.

Statistics

The new formula would be regarded as not inferior to the old formula if the geometric mean of antibody levels obtained at D 42 with the new formula was above 34.5% of the geometric mean of the antibody levels obtained at D 42 with the old formula. The lower limit of the one-

sided 97.5% confidence interval of the ratio of the geometric means (new formula/old formula) had to be above 0.354.

Results

Two hundred and fifty one subjects were included: 126 were vaccinated with the new formula and 125 with the old one. Two hundred and twenty one subjects were included in the per-protocol analysis.

The median age in the group receiving the new formula was 29, while that in the group receiving the old formula was 30.

The immunogenicity results are shown in *table 3*

Table 3: antibody titres

Test and vaccines (n patients)*	Geometric mean on D42 (95%CI)	Ratio of geometric means D42/D0 (95%CI)	Geometric mean on D56 (95%CI)	Ratio of geometric means D56/D0 (95%CI)
Neutralisation (internal) (n = 221) *				
New formula	43 (37-51)	43 (37-51)	41 (35-49)	41 (35-49)
Old formula	49 (42-59)	49 (42-59)	46 (39-55)	46 (39-55)
Neutralisation (Holzmann) (n = 34) *				
New formula	14 (10-18)	2.7 (2-3.6)	9.6 (7.4-12)	1.9 (1.5-2.5)
Old formula	11 (9-14)	2.2 (1.7-2.8)	11 (8.8-14)	2.2 (1.8-2.8)
ELISA (Enzygnost) (n= 221)				
New formula	21 (19-25)	6.3 (5.5-7.2)	21 (18-24)	6.2 (5.4-7.1)
Old formula	27 (23-31)	8.2 (7.2-9.4)	25 (21-28)	7.5 (6.5-8.6)

* the breakdown in the groups was not specified; CI: confidence interval;

Non-inferiority test:

The ratio of the geometric means between the new formula and the old formula on D42 was 0.88, and the lower limit of its 97.5% confidence interval was 0.69. As this value was higher than the non-inferiority limit, set at 0.354, the new formula was considered to be not inferior to the old formula.

The seroconversion rates for the individual tests are shown in *table 4*

Table 4: seroconversion rate

Test and vaccines (n patients)*	Seroconversions: % on D42 (95%CI)	Seroconversions: % on D56 (95%CI)
Neutralisation (internal) † (n= 221)*		
New formula	100% (97-100)	100% (97-100)
Old formula	100% (97-100)	100% (97-100)
Neutralisation (Holzmann) ‡ (n= 34)*		
New formula	87% (60-98)	53% (27-79)
Old formula	63% (38-84)	74% (49-91)
ELISA (Enzygnost) § (n= 221)*		
New formula	85% (77-91)	81% (73-88)
Old formula	76% (67-84)	78% (69-85)

CI: confidence interval; †: seroconversion if the titre prior to vaccination is <2 and on D42 ≥2;

‡: seroconversion if the titre prior to vaccination is <10 and on D42 ≥10; §: seroconversion if the titre prior to vaccination is <13 U/ml and on D42 ≥13 U/ml.

3.1.3 Study V48P5

Method

Randomised, double-blind study with two parallel groups (3/1) comparing the new formula of the vaccine ENCEPUR to the old formula in healthy adult volunteers aged 18 and over and adolescents aged 12 to 17.

Primary objective: to demonstrate the non-inferiority of the new formula compared to the old formula for the proportion of subjects experiencing moderate or severe malaise.

The injections were given on D0, D7 and D21.

Secondary objectives:

- To compare the safety of the two formulae
- To compare the immunogenicity of the new formula compared to the old formula 14 days after the 2nd injection (D21) and 21 days after the 3rd injection (D42); this immunogenicity study was performed only on the sub-group of adolescents aged between 12 and 17.
- To compare the seroconversion rates of the new formula compared to the old formula 14 days after the 2nd injection and 21 days after the 3rd injection.

Statistics

Non-inferiority was demonstrated if the upper limit of the 97.5% one-sided confidence interval of the proportion of cases of moderate or severe malaise following injection of the new formula was below that of cases of moderate or severe malaise observed following injection of the old formula + 5%.

Results

A total of 2,830 subjects were included: 2,118 in the group vaccinated with the new formula (group 1) and 712 with the old formula (group 2), all of whom received the first injection. 2,009 subjects in group 1 and 708 subjects in group 2 received the second injection. 2,008 subjects in group 1 and 702 subjects in group 2 received the third injection.

The average age of the subjects was 30.9 in group 1 and 31.5 in group 2.

These 2,830 subjects included 455 adolescents: 357 in group 1 and 98 in group 2.

Immunogenicity was investigated in the 114 adolescents who received the three injections.

The immunogenicity results, measured by a neutralisation test (test not specified) on adolescents (per-protocol analysis), are shown in *table 5*

Table 5: antibody titres in adolescents (PP analysis):

	Geometric mean of antibody titres (95%CI)	
	D21	D42
New formula (n= 90)	35 (29-42)	68 (58-79)
Old formula (n= 24)	39 (28-55)	50 (37-67)

CI = confidence interval;

Seroconversion was obtained if antibodies were undetectable on D0 but detectable on D42; under these conditions, seroconversion had occurred in 100% of the subjects included in the per-protocol population.

3.2. Adverse events

3.2.1 Study V48P1

Local and systemic post-injection reactions were recorded for 6 days after each injection. Other adverse events were recorded throughout the study.

The most common moderate to severe local post-injection reactions were pain at the injection site (50% of patients with the new formula, 32% with the old formula).

The most common moderate to severe systemic reactions were headache (27% of patients with the new formula, 18% with the old formula).

No serious adverse events occurred.

3.2.2 Study V48P2

Local and systemic post-injection reactions were recorded for 6 days after each injection. Other adverse events were recorded throughout the study.

The frequency of local and systemic post-injection reactions was similar in both groups. The frequency of these reactions fell as the course of injections progressed: 75% with the new formula and 73% with the old formula after the first injection, 61% with the new formula and 58% with the old formula after the second injection, 55% with the new formula and 51% with the old formula after the third injection.

The most common moderate to severe local post-injection reactions for all three injections were pain at the injection site (23% of patients vaccinated with the new formula, 25% with the old formula).

The most common moderate to severe systemic reactions were headache (18% of patients vaccinated with the new formula, 24% with the old formula) and cases of "malaise" (14% of patients vaccinated with the new formula, 20% with the old formula).

Two serious adverse events occurred, but were not considered to be related to the vaccination.

3.2.3 Study V48P5

Primary objective of the study: proportion of subjects experiencing at least one episode of moderate or severe malaise in the six days following an injection. The results are presented in *table 3*.

Table 3: Number of subjects experiencing moderate or severe malaise following injection

	n patients having at least one episode of malaise / n patients in group	% of patients (95%CI)
New formula	117 / 2133	6% (5-7%)
Old formula	58 / 711	8% (6-10%)

As the limit of the 97.5% confidence interval of the proportion of subjects experiencing moderate or severe malaise after receiving the new formula was 7%, i.e. below the acceptability limit of 13%, the new formula was considered not inferior to the old formula for this criterion.

The frequency of local and systemic post-injection reactions was similar in both groups. The frequency of these reactions fell as the course of injections progressed: 60% with the new formula and 61% with the old formula after the first injection, 50% with the new formula and 45% with the old formula after the second injection, 39% with the new formula and 38% with the old formula after the third injection.

The most common local post-injection reactions were mild to severe pain at the injection site after the first injection (45% in each group).

The most common mild to severe systemic reactions were myalgia and headache after the first injection, affecting 18% and 16% of patients receiving the new formula and 18% and 23% of those receiving the old formula.

The percentage of patients vaccinated with the new and old formulae who developed a fever within the six days following each injection, generally between 38 and 39°C, was less than or equal to 1%.

Five serious adverse events occurred, but were not considered to be related to the vaccination.

3.3. Conclusion

The rate of seroconversion obtained with the new formula of ENCEPUR at D42 after three injections performed on D0, D7 and D21 was between 75 and 100%, depending on the studies and the test used to measure immunogenicity. One study assessed the seroconversion rate at D56, and found it to be between 53 and 100% depending on the test used.

The most frequent adverse events were reactions occurring within six days after injection:

- local reactions: slight to severe pain at the injection site (23 to 50% of patients);
- moderate to severe systemic reactions: headache (16 to 27% of patients), malaise (14%), myalgia (18%);
- in one study, 1% of patients developed a fever, generally between 38 and 39°C, in the six days following vaccination.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Tick-borne encephalitis infections generally have few symptoms. The infection can cause a flu-like syndrome. Serious forms of encephalitis can lead to paralysis, which may have lasting consequences, or death.

This proprietary medicinal product is intended to provide prophylactic treatment.

The efficacy (immunogenicity)/adverse effects ratio is high.

Public health benefit:

The severity of tick-borne encephalitis (TBE virus) is related mainly to the neurological consequences it can cause. The number of cases involving neurological complications each year is low. They occur only in some parts of France, and no recent increase in the number of cases of TBE has been identified. In addition, the public health burden is at best small.

No public health need exists, given the possible alternatives and the lack of any official recommendation for people living in France to be vaccinated.

The data available is insufficient to allow any estimate to be produced of the number of patients who would need to be vaccinated in order to avoid one case. Consequently, it is impossible to quantify the expected impact in reducing morbidity and mortality associated with tick-borne encephalitis.

ENCEPUR is therefore not expected to have an impact on public health.

This proprietary medicinal product is a first-line therapy.

An alternative medicinal product exists (TICOVAC)

The actual benefit of this proprietary medicinal product is substantial.

4.2. Improvement in actual benefit (IAB)

ENCEPUR 1.5 µg/0.5 ml offers no improvement in actual benefit (IAB V) compared to TICOVAC.

4.3. Therapeutic use

According to the opinion produced by the Haut Conseil de la santé publique¹, in the light of the epidemiological data:

- vaccination with a vaccine against tick-borne encephalitis is recommended for people travelling to rural or forested areas in Central, Eastern and Northern Europe where the condition is endemic between spring and autumn.

- Prevention also depends on individual protection measures taken while hiking or camping in areas where the condition is endemic:

- clothes covering the whole body and fitting snugly at the neck, wrists and ankles,
- shoes or boots rather than sandals,
- clothing impregnated with insect repellent, or insect repellent applied to the skin,
- detailed examination of the entire body to remove ticks as quickly as possible.

¹ Opinion of the Haut Conseil de la santé publique dated 23 October 2009 on the use of Encepur in preventing central European tick-borne encephalitis:
http://www.hcsp.fr/docspdf/avisrapports/hcspa20091023_encephatiquence.pdf

- Systematic vaccination is not recommended for travellers against tick-borne encephalitis outside these situations or for people living in France².

4.4. Target population

The target population of individuals eligible for vaccination against tick-borne encephalitis consists of people travelling to rural or forested areas in Central, Eastern and Northern Europe where the condition is endemic between spring and autumn.

No estimate can be made as to the size of this population since no epidemiological data for these travellers is available.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for use by hospitals and various public services in the indications and dosages of the marketing authorisation.

The Transparency Committee regrets that no prospective studies have been carried out to compare the efficacy and safety of the proprietary medicinal product ENCEPUR 1.5 µg / 0.5 ml with the efficacy and safety of TICOVAC adultes.

4.5.1 Packaging: Appropriate for the prescription conditions.

² Opinion of the Haut Conseil de la santé publique dated 11 December 2009 on the minimum information requirements for publicity material relating to the tick-borne encephalitis vaccine Encepur[®]:

http://www.hcsp.fr/docspdf/avisrapports/hcspa20091211_encephatiquence.pdf