HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

OPINION

31 May 2006

TICOVAC 0.25 mL ENFANTS *[Ticovac 0.25 mL for children]*, suspension for injection in prefilled syringe. Tick-borne encephalitis vaccine (inactivated)
0.25 mL prefilled glass syringe with needle B/1: 367 749-9
0.25 mL prefilled glass syringes with needle B/10: 367 751-3

Applicant: Baxter SAS

tick-borne encephalitis virus (Neudoerfl strain)

Date of Marketing Authorisation:
TICOVAC 0.25 mL ENFANTS *[Ticovac 0.25 mL for children]*, suspension for injection in prefilled syringe.

Reason for application: 07 March 2005
TICOVAC 0.25 mL ENFANTS B/1: Inclusion on the list of products reimbursed by National Insurance and approved for use in hospitals
TICOVAC 0.25 mL ENFANTS B/10: Inclusion on the list of products approved for use in hospitals

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Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Tick-borne encephalitis virus (Neudoerfl strain) or TBEV (tick-borne encephalitis virus)

1.2. Background

This is a new presentation of Ticovac vaccine specifically adapted for use in children aged over 1 year and under 16 years.

1.3. Indications

Ticovac 0.25 mL Enfants is indicated for active (prophylactic) immunisation against tick-borne encephalitis virus in children aged over 1 year and younger than 16 years.

Ticovac 0.25 mL Enfants should be administered according to the official guidelines defining requirements and to the vaccination schedule against tick-borne encephalitis virus.

1.4. Dosage

The primary vaccination schedule for children aged over 1 year and under 16 years consists of 3 injections of Ticovac 0.25 mL Enfants.
The first injection should be given on a fixed date and the second should be given 1–3 months later. If a rapid immunological response is needed, the second injection may be given 2 weeks after the first one. The third injection should be given 5–12 months after the second one.

To confer immunity before the start of the tick activity season, i.e. the spring, the 1st and 2nd injections should ideally be given in winter. The third injection should be given before the start of the tick activity season.

If the intervals between the three injections (as given above) are exceeded, subjects may be inadequately protected against infection during these intervals (see sections 4.4 and 5.1).

Booster doses

The first booster dose should be given within three years of injection of the third dose (see section 5.1).

Booster doses may be given according to national guidelines, but not earlier than 3 years after the last booster dose. The recommended interval, based on epidemiological data and local experiences, is 3–5 years.

Children with immune deficiency (including children treated with immunosuppressants) : see SPC

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2005)

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. Comparator medicines

Ticovac 2.7 micrograms, suspension for injection in prefilled syringe. Tick-borne encephalitis vaccine, adsorbed (indicated in children over 3 years and adults)

2.2.2. Comparisons that have been carried out

Not applicable

2.3. Medicines with the same therapeutic aim

No other vaccines are currently available

3 ANALYSIS OF AVAILABLE DATA

3.1. Immunogenicity

The dossier contains 5 clinical trials:

- 2 dose-ranging studies: study 199 (extended by study 206 including a 3rd injection in the vaccination schedule) and study 205 (extended by study 207 which included a 3rd injection in the vaccination schedule)
- 2 noncomparative studies evaluating the immunogenicity and safety of the vaccine in different age ranges: study 198 (extended by study 215 which included a 3rd injection in the vaccination schedule) and study 209.
- postmarketing study carried out in Austria (study 197: page 80 of the technical dossier) assessing onset of febrile episodes after the 1st injection (tabulated summary not provided by the company.

The vaccination schedule used was: 2 injections 1–3 months apart and a 3rd injection 9–10 months after the 2nd injection.

Immunogenicity was assessed 3–5 weeks after the 2nd and 3rd injections. Seroconversion was classed as positive (depending on the study):

- when antibody titre was >126 Vienna Units (VIE U)/mL after the 2nd and 3rd injections (for patients with titre < 63 VIE U/mL at inclusion)
- when antibody titre had doubled after the 2nd and 3rd injections from baseline value measured at inclusion (for patients with titre between 63 VIE U/mL and 126 VIE U/mL at inclusion).

The endpoint was seroconversion rate after the 2nd and 3rd injections (percentage of vaccinated children seroconverted).

- Study 198 (open study/ immunogenicity and safety): children aged 1–12 years (N=101)* extended by study 215
- Study 199 (dose-ranging): children aged 1–6 years (N=201) extended by study 206
- Study 205 (dose-ranging): children aged 6–16 years (N=206) extended by study 207
- Study 209 (open study/safety): children aged 1–15 years (N=2381 including 373 patients included in assessment of immunogenicity)

*(The number of patients stated corresponds to the number of children who were vaccinated with Ticovac Enfant vaccine containing 1.2 mcg)

Results:

Seroconversion rate measured by an ELISA method in the different studies after the 2nd and 3rd injections (ELISA immunoenzymatic assay)

Trial no.	**Age**	**Seroconversion rate Ticovac 0.25 mL Enfants (1.2 mcg)**			
		2nd injection		**3rd injection**	
		n / N	%	n / N	%
198		100 /101	**99%**		
(215)	**1–12 yrs**			99 /99	**100%**
199	**1–6 yrs**	201 /201	**100%**		
(206)	**1–6 yrs**			199 /199	**100%**
205	**6–16 yrs**	203 /206	**98.5%**		
(207)	**6–16 yrs**			202 /202	**100%**
209	**1–16 yrs**	358 /373	**96%**		

More than 96% of vaccinated subjects had seroconverted 3–5 weeks after the second injection. Seroconversion rate after the third injection reached 100%.

3.2 Undesirable effects

In clinical trials, the following undesirable effects were reported after the 1st, 2nd and 3rd injections:
- onset of febrile episodes according to age of child and degree of severity of fever.
- local and systemic undesirable effects (other than fever)

I - Onset of febrile episodes:

Frequency of onset of fever in the different studies:

Trial	**Number of patients**	**Age**	**Cases of fever reported n(%)**		
			1st inj.	2nd inj.	3rd inj.
198	101	1–12 yrs	30(29.7%)	9 (8.9%)	
215	98	1–12 yrs			12(12.2%)
199	201	1–5 yrs	32 (15.9%)	32 (15.9%)	
206	200	1–5 yrs			22(11%)
205	206	6–15 yrs	7 (3.4%)	8 (3.9%)	
207	201	6–15 yrs			11 (5.5%)
209	183	1–2 yrs	66(36.1%)	23(12.6%)	
	559	3–6 yrs	72(12.9%)	13(2.3%)	
	1632	7–15 yrs	92(5.6%)	20(1.2%)	
	2374	Total	230(9.7%)	54(2.3%)	

Frequency of onset and severity of fever after the 1st and 2nd injections in **study 209**:

Age group	**Cases of fever reported** n/ N	**Fever** % (CI 95%)	**Severity of cases of fever reported** n (%)		
			Mild 38.0–39.0 ℃	Moderate 39.1–40.0℃	Severe > 40℃
1st injection					
1–2 yrs	66 / 183	36.1 (29.1; 43.5)	57 (31.1%)	9 (4.9%)	0 (0.0%)
3–6 yrs	72 / 559	12.9 (10.2; 15.9)	59 (10.6%)	13 (2.3%)	0 (0.0%)
7–15 yrs	92 / 1632	5.6 (4.6; 6.9)	90 (5.5%)	2 (0.1%)	0 (0.0%)
Total	230 /2374	9.7 (8.5; 11.0)	206 (8.7%)	24 (1.0%)	0 (0.0%)
2nd injection					
1–2 yrs	23 / 183	12.6 (8.1; 18.3)	22 (12.0%)	0 (0.0%)	1 (0.5%)
3–6 yrs	13 / 558	2.3 (1.2; 4.0)	11 (2.0%)	2 (0.4%)	0 (0.0%)
7–15 yrs	20 / 1636	1.2 (0.7; 1.8)	18 (1.1%)	1 (0.1%)	0 (0.0%)
Total	54 /2377	2.3 (1.7; 3.0)	51 (2.1%)	3 (0.1%)	1 (0.0%)

Frequency of onset of febrile episodes after the second injection was generally lower than that reported after the first injection.

Frequency of onset of febrile episodes was higher in children aged 1–2 years than in children aged 3–15 years (study 209),

- after the first injection: 36.1% in children aged 1–2 years; 12.9 % in children aged 3–6 years; 5.6% in children aged 7–15 years
- after the 2nd injection: 12.6% in children aged 1–2 years; 2.3% in children aged 3–6 years; 1.2% in children aged 7–15 years

Mild febrile episodes (fever 38–39℃) were more com mon than those of moderate severity (fever 39.1–40℃), irrespective of age.

II - Local undesirable effects at the injection site:

- Very common: pain and sensitivity at the injection site,
- Common: swelling, induration and erythema at the injection site.

III - Systemic undesirable effects (other than fever):

- Very common: headache,
- Common: nausea, vomiting, myalgia, arthralgia, anorexia, agitation, insomnia.

In very rare cases <1/10 000, encephalitis and febrile convulsions were observed in children under 3 years old after vaccination.

3.3 Conclusion

More than 96% of vaccinated subjects had seroconverted 3–5 weeks after the second injection. Seroconversion rate after the third injection reached 100%.

The frequency of onset of febrile episodes after the second injection was generally lower than that reported after the first injection.

Febrile episodes were more common in children aged 1–2 years than in children aged 3–15 years (study 209),

- after the first injection: 36.1% in children aged 1–2 years; 12.9 % in children aged 3–6 years; 5.6% in children aged 7–15 years
- after the 2nd injection: 12.6% in children aged 1–2 years; 2.3% in children aged 3–6 years; 1.2% in children aged 7–15 years

Mild febrile episodes (fever 38–39°C) were more common than those of moderate severity (fever 39.1–40°C), irrespective of age.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1 Actual benefit

Tick-borne encephalitis is a rare seasonal viral disease that can have incapacitating neurological sequelae and may in very rare cases be life-threatening.

Vaccination is an effective preventive measure.

The drug is given as preventive therapy.

Public Health Benefit

The severity of tick-borne encephalitis (TBE virus) lies mainly in the neurological sequelae that it may cause. Annual cases with neurological complications are rare; they are limited to certain parts of France and their number seems to have increased very little since Ticovac was made available for use in hospitals. The burden to public health is therefore clearly low.
Compared with current public health priorities and the absence of indication for official recommendation of Ticovac, except for travellers, there is no public health need.
In view of the available data which are insufficient for estimating the number of patients to be vaccinated to avoid one case, and in view of the difficulty in identifying individuals who could benefit from Ticovac, the expected impact on reduction in mortality and morbidity related to tick-borne meningitis and encephalitis cannot be quantified.
Consequently, as there are insufficient data, no public health benefit is expected for Ticovac.

There is only one vaccine (Ticovac 2.7 micrograms) which could be replaced by Enfant in children aged over 1 year and under 16 years.

The actual benefit of Ticovac Enfant is substantial in children aged over 1 year and under 16 years.

4.2 Improvement in actual benefit

Compared with the vaccine Ticovac 2.7 micrograms, the new Ticovac presentation differs in the following ways:
- composition: 0.1% human albumin has been added to reduce the high incidence of post-vaccine febrile reactions observed in Austria in March 2000 (more particularly in children aged under 3 years)
- dose: 1.2 micrograms (instead of a half dose of Ticovac 2.7 micrograms)
- vaccination schedule: the 3rd injection is given 5–12 months (instead of 9–12 months) after the 2nd injection
- the vaccination may be given after the age of one year (instead of 3 years).

Ticovac Enfant does not contribute any improvement in actual benefit (level V) compared with the vaccine Ticovac 2.7 micrograms which it would replace in children aged over 1 year and under 16 years.

4.3. Therapeutic use / vaccination against tick-borne encephalitis

Opinion of the French *Conseil supérieur d'hygiène publique*:

- Vaccination schedule (BEH[1] no. 29-30 / 2005):

At its meeting on 29 January 2004, the *Comité technique des vaccinations (CTV)*[2] felt that in view of the data presented by the *Institut de Veille Sanitaire*[3] and by the French national reference centre, there was no indication for official recommendation of this vaccine for certain parts of France. The vaccine should be prescribed on a case-by-case basis.

- Health guidelines for travellers (BEH no. 29-30 / 2005):

Staying in a rural area (or walking in forests) in Central, Western or Northern Europe, in the spring or summer.

4.4 Epidemiological data

Cases of tick-borne meningitis and encephalitis are still only rarely recorded in France: about 30 cases were recorded between 1968 and 1997, in Alsace, in the Vosges and in Lorraine.
According to expert opinion, 78 cases of infection with neurological meningeal complications were reported in Alsace between 1968 and 2006. The annual number of cases with neurological complications varies, between 3 and 5 a year.

4.5 Target population

It is not possible to estimate the target population as:

- the vaccine is to be prescribed to French residents on a case-by-case basis, in accordance with *Conseil Supérieur d'hygiène publique* guidelines.
- there are no epidemiological data that would provide a specific estimate of the population of travellers to be vaccinated in accordance with *Conseil Supérieur d'hygiène publique* guidelines.

4.6 Transparency Committee recommendations

The Committee notes that the presentation currently available, Ticovac 2.7 micrograms, is not reimbursed to people covered by National Insurance, and has only been approved for use in hospitals since 07 May 2000.
The epidemiological situation of tick-borne encephalitis (TBEV) has remained stable since that time, and the *Conseil supérieur d'hygiène publique* stated at its meeting on 29 January 2004 that there was no indication for official recommendation of this vaccine for certain parts of France, as the vaccine was to be prescribed on a case-by-case basis.

Consequently, in the current epidemiological situation, the Committee issues the following opinions:
B/1: Rejection of application for inclusion on the list of medicines reimbursed to people covered by National Insurance
B/1 and B/10: Approval of inclusion on the list of medicines approved for use in hospitals and various public services

[1] BEH: Bulletin Épidémiologique Hebdomadaire, the French weekly epidemiological bulletin
[2] Vaccinations technical committee
[3] French Institute for Healthcare Monitoring

In any case, the Committee would like information to be publicised to:
- remind people of non-pharmacological preventive measures such as preventing tick bites (by protecting the body), and removing ticks quickly.
- better target individuals exposed to bites from ticks carrying the TBE virus (tick-borne encephalitis virus)

In addition, the Committee would like information campaigns run by the company to be produced in cooperation with the French health authorities.

Packaging: the packaging is appropriate for the prescription conditions