TRANSPARENCY COMMITTEE

OPINION

26th April 2006

Fendrix, suspension for injection, hepatitis B vaccine (rDNA) (adsorbed, with adjuvant), B/1
1 prefilled syringe (glass) 0.5 mL with 1 needle: 365 867-4

Applicant: GlaxoSmithKline Biologicals SA

Hepatitis B surface antigen, recombinant (yeast/Saccharomyces cerevisiae)

List I

Date of Marketing Authorisation: 02/02/2005

Reason for application: Inclusion on the list of medicinal products reimbursed by National Insurance and approved for use by hospitals.
1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
Hepatitis B surface antigen, recombinant (yeast/Saccharomyces cerevisiae): 20 micrograms.

1.2. Background
This is a new vaccine against infection caused by all known subtypes of the hepatitis B virus, in patients aged 15 years and over with renal failure (including predialysis and dialysis patients). The vaccine contains a novel adjuvant, MPL (-3-O-desacyl-4’-monophosphoryl lipid A), adsorbed onto aluminium phosphate, an immune stimulator.

1.3. Indications
Fendrix is indicated for active immunisation against infection caused by all known subtypes of the hepatitis B virus, in patients aged 15 years and over with renal failure (including predialysis and dialysis patients).

1.4. Dosage
Primary vaccination schedule:
A four-dose schedule is recommended, with injections at 0, 1, 2 and 6 months.
Once started, primary vaccination at 0, 1, 2 and 6 months should be continued using the same vaccine and not with another commercially available vaccine against hepatitis B virus.

Booster:
As predialysis and dialysis patients are particularly at risk of infection with the hepatitis B virus, and at greater risk of chronic infection, a booster is recommended to ensure that the level of protective antibodies specified in national guidelines and directives is maintained.
Fendrix can be used as a booster after primary vaccination with Fendrix or another recombinant vaccine marketed for use against hepatitis B.

Special recommendations in patients with known or presumed exposure to hepatitis B virus:
There are no data on concomitant administration of Fendrix and specific immunoglobulins to hepatitis B (HBV Ig). However, if an individual has recently been exposed to the hepatitis B virus (e.g. needlestick injury with a contaminated needle), and if Fendrix has to be given concomitantly with a standard dose of HBV Ig, the injections should be given in different sites.

Mode of administration
Fendrix should be given as an intramuscular injection in the deltoid region.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2005)

J : GENERAL ANTI-INFECTIVES SYSTEMIC
J07 : VACCINES
J07B : VIRAL VACCINES
J07BC : VACCINES AGAINST HEPATITIS
J07BC01 : Hepatitis B, purified antigen
2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines (in adults)

- HBvaxPRO 40 micrograms/mL, suspension for injection in vial (presentation suitable for patients undergoing or awaiting dialysis): included only on the list for use in hospitals.
- Engerix B Vaccine 20 micrograms/mL adults, suspension for injection in prefilled syringe.
- Genhevac B Pasteur Vaccine 20 micrograms/0.5 mL, suspension for injection in prefilled syringe.
- HBvaxPRO 10 micrograms/mL, suspension for injection in vial and syringe.

2.2.2. Comparisons that have been carried out

Most used (number of treatment days): Engerix B20
(The percentage of prescriptions for renal failure is not known)
Most economical (cost of treatment): HBvaxPRO 10
Most recently added to the list: HBvaxPRO 10

2.3. Medicines with a similar therapeutic aim

(not applicable)

3 ANALYSIS OF AVAILABLE DATA / UPDATED DATA (PUBLISHED SINCE PREVIOUS OPINION)

3.1 Immunogenicity

The clinical dossier includes two studies of predialysis or dialysis patients, aged 15 years or over, with chronic renal failure (CRF):

I - comparative trial (HBV-MPL-032-042) to compare the immunogenicity of Fendrix and the Engerix B20 vaccine (2 doses) 7 months after primary vaccination, and persistence of the immune response at 12 months (trial HBV-MPL-042).

II - comparative trial (HBV-MPL-047), an extension of the HBV-MPL-032 trial, to assess persistence of the immune response compared with the Engerix B20 vaccine at 24, 30 and 36 months (after primary vaccination).

Subjects were aged 15 years or over at inclusion and were seronegative for HBs antigen, anti-HBs and anti-HBc antibodies.
Predialysis subjects were defined as those with creatinine clearance ≤ 30 mL/min (severe or terminal renal failure).

The primary endpoint was the level of seroprotection (SP): percentage of subjects with an anti-HBs antibody titre ≥ 10 mIU/mL (SP ≥ 10 mIU/mL), measured 1 month after the last dose of vaccine.

Secondary endpoints (measured 1 month after the last dose of vaccine):
- percentage of subjects with an anti-HBs antibody titre ≥ 100 mIU/mL (SP ≥ 100 mIU/mL),
- geometric mean antibody titre (GMT), assessed from antibody titres above the detectable threshold value (≥ 3.3 mIU/mL),
- number of patients needing a booster (subjects with an anti-HBs antibody titre < 10 mIU/mL after 24 months, 30 months).

I - Trial HBV-MPL-032-042: N = 165 (82 patients in the Fendrix group/ 83 patients in the Engerix B20 group). The primary vaccination dose schedule was 0, 1, 2 and 6 months.
The aim of the trial was to demonstrate the superiority of Fendrix compared with Engerix B20, in terms of immunogenicity after primary vaccination.

Results at 7 months (per-protocol analysis):
N = 165 (82 patients in the Fendrix group/ 83 patients in the Engerix B20 group)

Seroprotection level (SP ≥ 10 mIU/mL) was 90.9% in the Fendrix group and 84.4% in the Engerix B20 group (2 doses), difference not significant.
(Seroprotection level SP > 10 mIU/mL at 3 months, an intermediate result, was significantly higher in the Fendrix group than in the Engerix B20 group: 74.4% compared with 52.4%).
Seroprotection level (SP ≥ 100 mIU/mL) in the Fendrix group was significantly higher than in the Engerix B20 group (83.1% compared with 67.5%, p = 0.0389).
Geometric mean antibody titre (GMT) in the Fendrix group was significantly higher than in the Engerix B20 group (3559.2 mIU/mL compared with 933 mIU/mL, p = 0.0005).

Results at 12 months (per-protocol analysis):
(N = 141 (71 patients in the Fendrix group/ 70 patients in the Engerix B20 group)

Seroprotection level (SP ≥ 10 mIU/mL) was 85.9% in the Fendrix group and 77.1% in the Engerix B20 group (2 doses). This difference is not significant.
Seroprotection level (SP ≥ 100 mIU/mL) in the Fendrix group was significantly higher than in the Engerix B20 group (73.2% compared with 54.3%, p = 0.0231).
Geometric mean antibody titre (GMT) in the Fendrix group was significantly higher than in the Engerix B20 group (907 mIU/mL compared with 320.8 mIU/mL, p = 0.0037).
Results at 7 months and 12 months:
- for the primary endpoint (seroprotection level: SP \geq 10 \text{ mIU/mL})
- for a secondary endpoint (seroprotection level: SP \geq 100 \text{ mIU/mL})

<table>
<thead>
<tr>
<th>Seroprotection level</th>
<th>Fendrix Results at 7 months (%) (N = 82)</th>
<th>Engerix B20 Results at 7 months (%) (N = 83)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SP \geq 10 mIU/mL</td>
<td>90.9</td>
<td>84.4</td>
<td>NS</td>
</tr>
<tr>
<td>SP \geq 100 mIU/mL</td>
<td>83.1</td>
<td>67.5</td>
<td>0.0389</td>
</tr>
</tbody>
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<td>0.0231</td>
</tr>
</tbody>
</table>

NS: not significant

II – Trial HBV-MPL-047
(extension of the HBV-MPL-032 trial analysed up to 36 months after vaccination):
N = 91 (48 patients in the Fendrix group/ 43 patients in the Engerix B20 group)

The aim of the trial was to compare persistence of the immune response at 24, 30 and 36 months (i.e. 3 years after primary vaccination) with persistence after Engerix B20 vaccine in vaccinated patients from the HBV-MPL-032 trial. Patients without seroprotection, with an antibody level of < 10 mIU/mL, and who had received a booster, were included in the trial.

Results at 24, 30 and 36 months (intention to treat analysis):
N = 91 (48 patients in the Fendrix group/ 43 patients in the Engerix B20 group)

Seroprotection level
At 24 months, the seroprotection level (SP \geq 10 \text{ mIU/mL}) was 89.6% in the Fendrix group and 76.2% in the Engerix B20 group, difference not significant.
At 30 and 36 months, the seroprotection levels in the Fendrix group were significantly higher than in the Engerix B20 group:
- at 30 months: 84.8% vs. 62.5%
- at 36 months: 80.4% vs. 51.3%

Percentage of subjects with anti-HBs antibody titres \geq 100 \text{ mIU/mL} (SP \geq 100 \text{ mIU/mL}):
There was no significant difference between the results for the two groups:
- at 24 months: 66.7% in the Fendrix group and 52.4% in the Engerix B20 group
- at 30 months: 63% in the Fendrix group and 40% in the Engerix B20 group
- at 36 months: 58.7% in the Fendrix group and 38.5% in the Engerix B20 group

Geometric mean titre:
There was no significant difference between the GMT in the Fendrix group and that in the Engerix B20 group at 24, 30 and 36 months.
The number of vaccinated patients needing a booster during the follow-up period (anti-HBs antibody titre < 10 mIU/mL) was significantly lower in the Fendrix group (11/62 patients vs. 22/57 patients, i.e. 18% vs. 38.5%, p < 0.05).

3.2 Undesirable effects

In the HBV-MPL-032/-042 trial, the incidence of solicited (listed in advance) local and/or general symptoms was higher in the Fendrix group (54.2%) than in the Engerix B20 group (40.5%).

In the HBV-MPL-047 trial, the incidence of solicited local and/or general symptoms was similar in both groups (60% vs. 66.7%).

In the HBV-MPL-032 trial, the incidence of solicited local symptoms was higher in the Fendrix group than in the Engerix B20 group (41.8% vs. 18%):
- pain at the injection site was the commonest solicited local symptom reported in both groups, with a higher incidence in the Fendrix group (41%) than in the Engerix B20 group (13.2%).
- the incidence of redness and swelling was similar in both vaccine groups.

The incidence of grade 3 pain was comparable in both groups (0.7% of Fendrix doses compared with 0.6% of Engerix B20 doses).

Reactogenicity after the booster was no higher than that observed after the primary vaccination doses.

A similar incidence of solicited general symptoms was observed in the two groups, with tiredness being the most commonly reported symptom (16.7% vs. 16.4%).

Few grade 3 general symptoms were reported (< 2% of doses of Fendrix compared with < 1% of doses of Engerix B20).

In each vaccine group, the majority of local and general symptoms resolved during the 4-day follow-up period.

3.3 Conclusion

In patients with severe or terminal renal failure (glomerular filtration rate \( \leq 30 \text{ mL/min} \)), Fendrix vaccine was not significantly better in terms of immunogenicity than Engerix B20 vaccine when judged on the primary endpoint of seroprotection level (percentage of subjects with an anti-HBs antibody titre \( \geq 10 \text{ mIU/mL} \)) at 7 and 12 months after the first primary vaccination dose.

In contrast, after 36 months of follow-up the seroprotection level in the Fendrix group was significantly higher than that in the Engerix B20 group.

Furthermore,

1 – for the secondary endpoints, the results were statistically in favour of the Fendrix vaccine, for:
- geometric mean titre at 7 and 12 months
- percentage of subjects with an anti-HBs antibody titre \( \geq 100 \text{ mIU/mL} \) at 7 and 12 months (according to some authors, an anti-HBs antibody titre \( \geq 100 \text{ mIU/mL} \) should protect the majority of patients for at least one year)
- number of vaccinated patients needing a booster during the 36 months of follow-up (anti-HBs antibody titre < 10 mIU/mL)

2 - for an intermediate endpoint: the percentage of subjects with an anti-HBs antibody titre \( \geq 10 \text{ mIU/mL} \) was statistically higher in the Fendrix group 3 months after the first primary vaccination dose (74.4% vs. 52.4%).
Fendrix vaccine caused transient local symptoms (pain at the injection site) more often than the Engerix B20 vaccine. General symptoms were observed with a similar frequency in both groups.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Hepatitis B can develop into a chronic disease and can be life-threatening. Predialysis and dialysis patients are at increased risk of infection and of chronic disease (60% compared with 5–10% of healthy patients).

This medicinal product is to be used as preventative treatment.

The efficacy/safety ratio is high.

There are other vaccines already on the market for the same preventative indication.

In patients with renal failure, hepatitis B represents a minor burden on public health. In public health terms there is a requirement for a vaccine which is able to produce a rapid and lasting immune response in patients with renal failure. In view of the results of these studies, Fendrix could meet part of this requirement.

Although the seroprotection level at 36 months is higher with Fendrix than with Engerix B20, Fendrix is not expected to have any impact on hepatitis B-related morbidity and mortality in patients with renal failure.

In view of the possible contribution to public health requirements, it is therefore expected that Fendrix will benefit public health. This benefit is minor.

The benefit of this medicinal product is substantial.

4.2. Improvement in actual benefit

Although Fendrix was not found to be statistically significantly superior to Engerix B20 in terms of the percentage of subjects with an anti-HBs antibody titre ≥ 10 mIU/mL (primary endpoint) at 7 and 12 months after the first vaccination dose, the results are in favour of Fendrix for:

- the clinically relevant secondary endpoints of rapid achievement of seroprotection at 3 months, and percentage of patients with anti-HBs antibody titres ≥ 100 mIU/mL,
- persistence of vaccine response at 36 months.

This vaccine should help improve vaccine coverage for predialysis and dialysis patients with renal failure.

However, local tolerance is less good (pain at the injection site).

The committee therefore feels that Fendrix offers a minor improvement in actual benefit (level IV) in terms of immunogenicity compared with the Engerix B20 vaccine in predialysis and dialysis patients with chronic renal failure and a glomerular filtration rate ≤ 30 mL/min.
4.3. Therapeutic use

The French Conseil supérieur d'hygiène publique recommends vaccination against hepatitis B in dialysis patients and patients with renal failure. Patients with chronic renal failure undergoing dialysis have their serological status checked annually. A booster is recommended to ensure a protective level of antibodies.

Diagnosis of chronic renal failure in adults and role of vaccination (ANAES Guidelines Department, September 2002)
Vaccination is recommended as soon as the moderate stage of renal failure is reached, i.e. in patients with a glomerular filtration rate < 60 mL/min.

The committee emphasises that a nephrologist should decide whether vaccination with Fendrix is appropriate in patients with progressive renal failure, for whom dialysis is planned.

4.4. Target population

The target population for Fendrix consists of:
- dialysis patients not immunised against hepatitis B or with non-seroprotective antibody levels (terminal stage of chronic renal failure: glomerular filtration rate < 15 mL/min/1.73 m²),
- predialysis patients not immunised or with non-seroprotective levels of antibodies against hepatitis B (severe stage of chronic renal failure: glomerular filtration rate 15–30 mL/min/1.73 m²).

1 - Dialysis patients

The number of patients with terminal renal failure treated by dialysis is thought to be around 30 000 (SROS-IRCT [Regional Health Organisation Plan - terminal chronic renal failure] national survey carried out in June 2003 by the State Health Insurance system: BEH [Weekly Epidemiological Record] no. 37-38/2005).

This estimate includes two subpopulations:
- Newly-diagnosed incident patients:
The incidence of patients with terminal chronic renal failure is thought to be around 100 per million inhabitants, i.e. 6000 new cases per year (Jungers P et al. Epidemiology of end stage renal disease in the Ile de France area: a prospective study in 1998. Nephrol Dial Transplant 2000;15:2000-2006).
According to the authors, the percentage of these patients who are not vaccinated and who receive emergency care is around 35%, i.e. 2100 people.

- dialysis patients (prevalent cases), representing around 24 000 patients being managed.
  it is thought that around 80–90% of these patients have been vaccinated, 20% of whom no longer have seroprotection (expert opinion), representing around 4000 patients/year, i.e. 1/5 of patients losing their immunity every year.
  around 10–20% of these patients will not have been vaccinated, i.e. 3600 patients.

The total estimated target population of patients with terminal renal failure is around 10 000.
2 - Predialysis patients

The estimated number of patients with non-terminal chronic renal failure, i.e. in the moderate and severe stages, is between 1.74 and 2.5 million (report by the *Groupe Technique National de Définition des Objectifs de santé publique*, 2003). These data do not distinguish between patients with moderate and severe chronic renal failure. It is therefore difficult to quantify the target population for Fendrix among predialysis patients with severe chronic renal failure using these data.

However, it is possible to form an idea of this population:
- either from the number of patients in whom creation of an arteriovenous fistula is envisaged (no useful data available),
- or from the number of patients starting dialysis (incident cases), given that progression from the severe stage of chronic renal failure to the terminal stage is rapid, taking around one year (expert opinion).

Using this second approach, the number of patients with severe chronic renal failure would be around 6000.

4.5. Transparency Committee recommendations

The Committee recommends inclusion on the list of medicinal products reimbursed by National Insurance and on the list of medicaments approved for use by hospitals, for the indication and at the dosage specified in the Marketing Authorisation.

**Packaging:** The packaging is appropriate for the conditions under which it is prescribed.

**Reimbursement rate:** 65%.