ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PRIMAVAX
Diphtheria, tetanus and hepatitis B (recombinant) vaccine, adsorbed

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Components	Unit formula
- Purified Diphtheria toxoid (formaldehyde- detoxified Diphtheria toxin)	≥ 30 IU
- Purified Tetanus toxoid (formaldehyde- detoxified Tetanus toxin)	≥ 40 IU
- Recombinant* Hepatitis B Surface Ag	5 μg
Aluminium hydroxide**	0.25 mg
Thiomersal	0.0435 mg
Sodium borate	8.75 μg
Acetic acid or sodium hydroxide	q.s. pH 6.5 ± 0.1
Buffered saline solution***	0.1 ml
Water for injections	up to 0.5 ml

* *Saccharomyces cerevisiae* strain 2150-2-3
** Expressed as Al+++
*** Buffered saline solution : sodium chloride, disodium phosphate dihydrate, potassium dihydrogen phosphate, water for injections

3. PHARMACEUTICAL FORM

Suspension for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This vaccine is indicated for active immunization against hepatitis B, caused by all known subtypes, diphtheria and tetanus in infants :
- for primary vaccination
- for booster
according to national vaccination policies.

This vaccine should not be administered to neonates.

This vaccine is not intended for use in adolescents or adults.

4.2 Posology and method of administration

Posology :
A series of three injections of vaccine is recommended (see schedule below). The first two injections may be considered priming doses, while the third may serve to boost the antibody

response in previously primed vaccinees or to seroconvert a small proportion that may be immunologically hyporesponsive to vaccine antigen. Clinical studies have been conducted following a three dose schedule as follows:

First injection : 0.5 ml dose during the 3rd month of life
Second injection : 0.5 ml dose during the 5th month of life
Third injection (booster) : 0.5 ml dose during the 11th month of life

Method of administration :
The vaccine should be administered by deep intramuscular injection. The anterolateral thigh is the preferred site for injection in infants.

The intradermal, intravenous or subcutaneous routes must not be used.

Simultaneous vaccination :
See 4.5

4.3 Contra-indications

- Usual contra-indications for any immunization : vaccination should be postponed in the case of fever or acute disease,
- Hypersensitivity to any component of the vaccine or severe reaction after previous administration of the vaccine.

4.4 Special warnings and special precautions for use

Do not administer by intravascular injection : ensure that the needle does not penetrate a blood vessel.

Because of the long incubation period of hepatitis B, it is possible for unrecognised hepatitis B infection to be present at the time of immunization. The vaccine may not prevent hepatitis B infection in such cases.

The vaccine will not prevent other hepatitis infection caused by other agents such as hepatitis A, hepatitis C and hepatitis E or by other liver pathogens.

As with all vaccines, appropriate medical treatment should be readily available for immediate use in case of anaphylactic reactions following the injection.

This vaccine contains thiomersal as a preservative.

The immunogenicity of the vaccine could be impaired by immunosuppressive treatment or immunodeficiency. It is recommended to postpone the vaccination until the end of the disease or the treatment. Nevertheless, vaccination of subjects with chronic immunodeficiency such as HIV infection is recommended even if the antibody response might be limited.

In infants with bleeding disorders such as haemophilia and thrombocytopenia, special precaution should be taken against the risk of haematoma following the injection.

4.5 Interaction with other medicinal products and other forms of interaction

This vaccine would appear not to interfere with the immune response following the concomitant administration of oral polio vaccine.

Although the concomitant administration of PRIMAVAX with other paediatric vaccines has not specifically been studied, it is commonly accepted opinion concerning vaccine associations, that PRIMAVAX could be administered simultaneously with other paediatric vaccines at different injection sites.

In any event the vaccine must not be mixed in the same syringe with other vaccines or parenterally administered drugs.

4.6 Use during pregnancy and lactation

Not applicable : this vaccine is only intended for pediatric use.

4.7 Effects on ability to drive and use machines

Not applicable : this vaccine is only intended for pediatric use.

4.8 Undesirable effects

In a phase II clinical trial, infants were monitored for local reactions for 3 days after injection and undesirable effects from the first injection up to one month after booster.
During the clinical study, the following undesirable effects reported in the first 3 days after any injection were :

- *Local reactions at the injection site (common (>1 %)) :*
  - pain,
  - redness,
  - induration occurring within 72 hours and persisting for one or two days,
  - nodules.

- *Systemic reactions (common (>1 %)) :*
  - transient hyperthermia (> 38 °C) associated or not with local reaction,
  - irritability,
  - drowsiness,
  - unusual crying
  - vomiting
  - diarrhoea.

No serious adverse event has been reported as related to vaccination.

The following undesirable effects have been reported following the widespread use of Pasteur Mérieux MSD Diphtheria-Tetanus and Hepatitis B recombinant vaccines:

⇒ for Pasteur Mérieux MSD Diphtheria-Tetanus vaccine :

- *Local reactions at the injection site :*

Pain, rash, induration or oedema can occur within 48 hours and persist for one or two days. The formation of a subcutaneous nodule can sometimes be observed. Aseptic abscesses have rarely been reported.
The incidence and severity of these local reactions may be influenced by the site, route and method of administration and the number of previous doses received.

- *Systemic reactions :*

Transient hyperthermia isolated or associated with a local reaction or lymphadenopathy, myalgia, arthralgia and headache may occur.

Immediate hypersensitivity reactions such as generalized pruritus, urticaria or oedema, feeling of dizziness, low blood pressure are exceptional.

Neurological disorders have rarely been observed and a causal relationship has not been demonstrated.

⇒ for Pasteur Mérieux MSD Hepatitis B recombinant :
As with other hepatitis B vaccines, in many instances, the causal relationship to the vaccine has not been established.

- *Common reactions (> 1 %) :*

local reactions at the injection site: transient soreness, erythema, induration

- *Rare reactions (< 0.1 %)* :

- elevation of liver enzymes, fatigue, fever, malaise, influenza-like symptoms, broncospasm-like symptoms, serum sickness, thrombocytopenia
- dizziness, headache, paresthesia
- nausea, vomiting, diarrhoea, abdominal pain
- arthralgia, myalgia
- rash, pruritis, urticaria, anaphylaxis
- hypotension, syncope
- paralysis(Bell's palsy), neuropathy, neuritis (including Guillain Barre Syndrome, myelitis (including transverse myelitis)), encephalitis, optic neuritis
- angioedema, erythema multiforme
- lymphadenopathy

4.9 Overdose

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group : bacterial and viral vaccines combined, ATC code : J07CA

The diphtheria and tetanus toxoids are prepared from the toxins of cultures of *Corynebacterium diphtheriae* and *Clostridium tetani,* formaldehyde detoxified then purified. The surface antigen of hepatitis B (HBsAg) virus is produced by culture of genetically - engineered yeast cells (*Saccharomyces cerevisiae)*.

This vaccine induces specific humoral antibodies against HBsAg (anti-HBs) and against diphtheria and tetanus toxoids (anti-D and anti-T). Development of anti-HBs titre above 10 mIU/ml and of anti-D and anti-T above 0.01 IU/ml measured 1-2 months after the third injection correlates with protection against hepatitis B virus infection and against diphtheria and tetanus diseases.

In clinical trials, 98 % of healthy infants given a 3 dose course of PRIMAVAX developed protective levels of anti-HBs (≥10 mIU/ml), and 100% of them developed protective levels of anti-D and anti-T (≥0.01 IU/ml).

5.2 Pharmacokinetic properties

Not applicable

5.3 Preclinical safety data

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Aluminium hydroxide,
- Thiomersal,
- Acetic acid or sodium hydroxyde,
- Sodium chloride,
- Disodium phosphate dihydrate,
- Potassium dihydrogen phosphate
- Sodium borate
- Water for injections.

6.2 Incompatibilities

The vaccine should not be mixed in the same syringe with other vaccines or parenterally administered drugs.

6.3 Shelf-life

The expiry date of the vaccine is indicated on the label and packaging.
When stored under prescribed conditions of temperature between +2°C and +8°C (in a refrigerator), the shelf-life is three years.

6.4 Special precautions for storage

Store between + 2°C and + 8°C.
Do not freeze.

6.5 Nature and content of container

0.5 ml suspension in syringe (glass) with a plunger stopper (chlorobutyl).

6.6 Instructions for use, handling and disposal (if appropriate)

Before use, the vaccine should be well shaken in order to obtain a homogeneous slightly opaque white suspension.

7. MARKETING AUTHORIZATION HOLDER

PASTEUR MERIEUX - MSD

8, rue Jonas SALK
69367 LYON Cédex 07
FRANCE

8. NUMBER IN THE COMMUNITY REGISTER OF THE MEDICINAL PRODUCTS

EU/1/97/056/001

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF AUTHORIZATION

5 February 1998

10. DATE OF REVISION OF THE TEXT