COMPANY CORE DATA SHEET – CCDS (EDS/CORE/ENGLISH)

HEPATITIS B IMMUNOGLOBULIN P BEHRING

Rev.: **02-JAN-2007** / CSL Behring

Supersedes previous versions
Rev.: 19-JUN-2006 / 6.3
Rev.: 02-MAY-2006 / Virus safety

1. NAME OF THE MEDICINAL PRODUCT

Hepatitis B Immunoglobulin P Behring

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 Qualitative composition

Human hepatitis B immunoglobulin

2.2 Quantitative composition

1 ml contains:

human protein		100 - 170	mg
thereof immunoglobulin	at least	95	%
with antibodies to HBs antigen	at least	200	IU

3. PHARMACEUTICAL FORM

Solution (ready-for-use) for intramuscular administration.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

– Prophylaxis of hepatitis B in
  a) all persons, from birth onwards, who are exposed to an increased risk of infection, preferably as simultaneous prophylaxis along with a hepatitis B vaccine.

  Prophylaxis of hepatitis B exposure (acc. the recommendations of the German Standing Advisory Committee on Vaccinations)
  Known non-responders (no measurable anti-HBsAg after at least 6 vaccinations) immediately receive hepatitis B vaccine and hepatitis B immunoglobulin.

  All other persons:

Number of previous hepatitis B vaccinations	anti-HBsAg level (is available within 24 hours)①	Administration required	
		hepatitis B vaccine	hepatitis B immunoglobulin
unknown, none, 1 or 2 (none or incomplete basic immunization)②	–	yes	yes
	> 100 IU/L	yes	no
3 or more	< 10 IU/L	yes	yes
	10 IU/L - 100 IU/L	yes	no
	> 100 IU/L	no	no

① If it is not possible to determine the anti-HBsAg level within 24 hours, a simultaneous prophylaxis (vaccine and immunoglobulin) is required in any case.
② Missing vaccinations of the basic immunization are to be completed according to the recommendations for the basic immunization.

A particular risk of infection exists, for example, in the following cases:
- through contact with HBsAg-positive material as a result of injury (prick, cut) or through contact with the mucous membranes (oral contact, splash into the eye). This particularly concerns medical personnel without protection who handle such material.
- close contact (even brief contact) with persons suffering from hepatitis B (e.g. members of the family, intimate contacts).
- neonates whose mothers contracted hepatitis B after the 1st trimester of pregnancy, or who are/were HBsAg-positive.
- transfusions of blood or blood components when HBsAg could not be precluded by sensitive test methods (e.g. during surgery, in dialysis patients).

b) Persons who are unable to develop adequate protection (e.g. dialysis patients) and who are exposed to a continual risk of infection (e.g. members of the family or intimate contacts to HBsAg-positive persons).

4.2 Posology and method of administration

4.2.1 Posology

a) For simultaneous prophylaxis administer 0.06 ml/kg body weight (bw) at the same time as the first injection of vaccine. For simultaneous prophylaxis in neonates a total dose of 1 ml of Hepatitis B Immunoglobulin P Behring should be used.

If no simultaneous prophylaxis is given (initially only vaccination), no less than – dependent on the anti-HBsAg level (see Table in 4.1)– 0.06 ml/kg bw of Hepatitis B Immunoglobulin P Behring have to be administered as soon as possible after exposure. Repeat the injection 4 weeks later using the same dose.

In cases of massive exposure (e.g. following a transfusion of blood or blood components when HBsAg could not be precluded by sensitive test methods), the immunoglobulin should be administered preferably in at least double the dose, i.e. at least 0.12 ml/kg bw is indicated.

b) for continuous prophylaxis administer 0.06 ml/kg bw every 3 months.

4.2.2 Method of Administration

If a rapid protection is required, prior anti-HBsAg testing can be omitted (see also table in 4.1)

Hepatitis B Immunoglobulin P Behring is a clear solution. The color can vary from colorless to pale-yellow up to light brown during shelf life. It is a ready-for-use solution and should be administered at body temperature, preferably ventrogluteally with the patient lying down.

Injections of Hepatitis B Immunoglobulin P Behring must be given by the intramuscular route only. Note that there is an increased risk of unintentional intravascular injection in patients who have repeatedly received intramuscular injections.

Do not inject intravascular! (see also 4.4)

If comparatively large doses are required it is advisable to administer them in divided fractions. This applies in the case of doses above 2 ml for children up to 20 kg bw and doses above 5 ml for persons above 20 kg bw.

In case of simultaneous prophylaxis the injections are to be administered at two different sites of the body with separate lymphatic drainage areas. The immunoglobulin is to be used with the first vaccination. Simultaneous prophylaxis should, as far as possible be given before exposure, otherwise immediately after exposure.

4.3 Contraindications

In patients with severe platelet deficiency or other coagulation disorders in the case of which intramuscular injections are contraindicated, Hepatitis B Immunoglobulin P Behring must not be administered.

Hypersensitivity to medicinal products containing homologous immunoglobulins, particularly in patients with IgA deficiency and concurrent presence of antibodies to IgA.

4.4 Special warnings and special precautions for use

Patients should be observed for at least 20 minutes after administration of Hepatitis B Immunoglobulin P Behring.

Do not inject intravascular!
An intravascular injection may cause the patient to develop shock-like symptoms, especially in case of antibody-deficiency syndrome. Therefore it is recommended to ensure by aspiration that no vessel has been penetrated.

The preparation is not suitable for treatment of hepatitis B infection.
Patients in the case of whom continuous prophylaxis is indicated, should be under continuous medical supervision. Prior to every injection a quantitative antibody determination (anti-HBsAg) by using a standard preparation should be done. If a passive-active immunization (latent immunity) has occurred, further injections can be omitted.

Virus safety
When medicinal products prepared from human blood or plasma are administered, infectious diseases due to the transmission of infective agents cannot be totally excluded. This also applies to pathogens of hitherto unknown nature.

To reduce the risk of transmission of infective agents, stringent controls are applied to the selection of donors and donations. In addition, virus elimination/inactivation procedures are included in the production process of Hepatitis B Immunoglobulin P Behring.

- Hepatitis B Immunoglobulin P Behring is prepared exclusively from plasma donations which have been tested negative for antibodies to HIV-1, HIV-2, HCV and for HBs antigen.
- In addition, the plasma pool is tested for antibodies to HIV-1, HIV-2, and for HBs antigen as well as for virus genetic material of HBV, HCV and HIV-1 using Nucleic acid Amplification Technology (NAT), e.g. Polymerase Chain Reaction (PCR). The latter is a very sensitive test method by which – in contrast to antibody testing - a direct test on virus genetic material is possible. The plasma pool is used for further processing only if the results of all these tests are negative.
- The production process of Hepatitis B Immunoglobulin P Behring contains various steps which contribute towards the elimination/inactivation of viruses. These include the use of a modified Cohn fractionation process and the heat treatment of the preparation in aqueous solution at 60 °C for 10 hours.

4.5 Interactions with other medicinal products and other forms of interactions

4.5.1 Vaccinations

After administration of immunoglobulins, an interval of at least 3 months should be allowed before vaccination with parenteral live virus vaccines (e.g. mumps, measles, rubella and the relevant combination vaccines as well as varicella vaccine). This is because the antibodies contained in Hepatitis B Immunoglobulin P Behring will otherwise inhibit viral multiplication which is necessary for the success of the vaccination.

No interval is required with regard to the following vaccinations:

- Live, oral vaccines (e.g. against poliomyelitis, typhoid fever) as these vaccines generate immunity primarily in the intestine.
- Vaccines containing inactivated pathogens (e.g. influenza, TBE, rabies, pertussis, HIB vaccines) or toxoid vaccines (e.g. diphtheria, tetanus and the relevant combination vaccines).

4.5.2 Interference with serological testing

When serological tests are performed after the administration of immunoglobulins, it should be remembered that immunoglobulin concentrates provide the patient with a wide range of antibodies which may lead to false-positive results for some time. When such antibody assays are carried out, the amount of immunoglobulin administered, the length of time between the administration of the immunoglobulin and the test, and the sensitivity of the test method should be taken into account.

4.6 Pregnancy and lactation

The safety of Hepatitis B Immunoglobulin P Behring for use in human pregnancy has not been established in controlled clinical trials. Therefore caution must be exercised if Hepatitis B Immunoglobulin P Behring is administered to pregnant or breast-feeding women. Long lasting clinical experience with immunoglobulins, in particular the routine application of anti-D-immunoglobulin, does indicate that no harmful effects on the course of pregnancy, on the foetus or the neonate are to be expected.

4.7 Effects on ability to drive and use machines

There are no indications that Hepatitis B Immunoglobulin P Behring may impair the ability to drive or use machines.

4.8 Undesirable effects

Occasionally, transient tenderness at the injection site, cutaneous reactions and elevations of temperature may occur.

In rare cases nausea, vomiting and also circulatory reactions (e.g. tachycardia, bradycardia, hypotension, sweating, vertigo) and allergoid/anaphylactoid reactions (e.g. with flush, urticaria, dyspnoea) have been observed. In isolated cases symptoms reaching as far as shock may occur, particularly if the product is inadvertently injected intravascular.

Allergoid/anaphylactoid reactions to immunoglobulin given in the prescribed intramuscularly manner are rare. On suspicion of an allergoid/anaphylactoid reaction the administration of Hepatitis B Immunoglobulin P Behring has to be discontinued immediately and an appropriate treatment has to be initiated. The current medical standards for shock treatment are to be observed.

As necessary, additional treatment should be given as follows:
a) Mild reactions: Administer corticosteroids and antihistamines.
b) Severe or life-threatening reactions (e.g. anaphylactic shock), depending on the severity of the reaction:
   – Immediately inject adrenaline slowly i.v.,
   – plus high doses of corticosteroids slowly i.v.,
   – if necessary volume replacement, oxygen.

Particularly in cases of inadvertent i.v. injections, patients should be observed for longer term (at least 1 hour) after administration.

4.9 Overdose

No symptoms of overdosage are known so far.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

5.1.1 Pharmaco-therapeutic group
Hepatitis B immunoglobulin
ATC-code: J06B B04

5.1.2 Pharmacodynamics
The action of Hepatitis B Immunoglobulin P Behring is based on neutralisation of viruses by antibodies in the blood and extracellular space.

5.2 Pharmacokinetic properties

Absorption of intramuscularly administered immunoglobulin from the injection depot commences approx. 20 min after application. The maximum blood level reached depends on age and physical condition and is generally achieved after 2 to 6 days following injection. The half-life of hepatitis B immunoglobulin amounts on average to 3 weeks.

5.3 Preclinical safety data

5.3.1 General toxicity

Immunoglobulins are normal constituents of the human body. Single dose toxicity testing is of no relevance since higher doses result in protein overload in the animals. Repeated dose toxicity testing in animals is impracticable due to induction of and interference with antibodies against heterologous protein.

5.3.2 Mutagenicity

Since clinical experience provides no hint for tumorigenic and mutagenic effects of immunoglobulins, experimental studies, particularly in heterologous species, are not considered imperative.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aminoacetic acid (glycine), sodium chloride, HCl or NaOH (in small amounts for pH adjustment), water for injections

6.2 Incompatibilities

Hepatitis B Immunoglobulin P Behring must not be mixed with other medicinal products.

6.3 Shelf life

36 months
Once an ampoule/prefilled syringe has been opened its contents are to be used immediately.

6.4 Special precautions for storage

Hepatitis B Immunoglobulin P Behring is to be stored at +2 to +8 °C. Do not freeze!

Keep out of the reach of children!

6.5 Nature and contents of container

6.5.1 Immediate containers
ampoule of colourless tube glass (Type I, Ph.Eur.)
SCF syringe of colourless tube glass, glass type I according to Ph. Eur.

6.5.2 Presentations
Pack with 1 ampoule of 1 ml
Pack with 1 prefilled syringe of 1 ml
Pack with 1 ampoule of 5 ml

6.6 Instructions for use/handling

Hepatitis B Immunoglobulin P Behring must not be used after the expiry date given on the pack and container.
Do not use solutions which are cloudy or contain residues (deposits/particles).
Hepatitis B Immunoglobulin P Behring is ready-for-use and should be administered at body temperature.

7. MARKETING AUTHORIZATION HOLDER

CSL Behring GmbH
Emil-von-Behring-Str. 76
35041 Marburg
Germany

8. MARKETING AUTHORIZATION NUMBER

– country specific–

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

– country specific –

10. DATE OF (PARTIAL) REVISION OF THE TEXT

January 2007