DIRECTORATE FOR PHARMACEUTICAL POLICY AND MONITORING
Strategy and Sustainability Division
Ministry for Social Policy

MSOC/HEC Circular No 84/2008
Ref df05/08

18th August 2008

Attention all Consultants
Medical Officers
Pharmacists
Nurses

Re: Human Anti-D Immunoglobulin

Kindly note that Human Anti-D Immunoglobulin Injections are currently available as 1250 IU pre-filled syringes (Partobulin SDF®). Human Anti-D Immunoglobulin Injections were previously available as 1500 IU vials (D-GAM®).

Please refer to the Summary of Product Characteristics for the change in dose.

For your attention please

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Director
DPPM

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Annex 1

Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

PARTOBULIN SDF
Human anti-D immunoglobulin for intramuscular use

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 preloaded syringe of PARTOBULIN SDF (1 ml) contains:

active ingredients
anti-D antibody 250 micrograms = 1250 IU
human protein 100-170 mg/ml
(of which at least 90% is immunoglobulin)

The amount of anti-D immunoglobulin contained in PARTOBULIN SDF is determined according to the method described in the European Pharmacopoeia.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Human anti-D immunoglobulin for intramuscular use is supplied in a liquid form. The solution comes in preloaded syringes.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of Rh(D) immunization in Rh(D) negative women

- Pregnancy/delivery of a Rh(D)-positive baby.
- Abortion/threatened abortion, ectopic pregnancy or hydatidiform mole
- Transplacental hemorrhage (TPH) resulting from antepartum hemorrhage (APH), amniocentesis, chorionic biopsy or obstetric manipulative procedure e.g. external version, or abdominal trauma.

Treatment of Rh(D) negative persons after incompatible transfusions of Rh(D) positive blood or erythrocyte concentrate.

4.2 Posology and method of administration

Posology

Postpartum prophylaxis:
The recommended standard dose ranges between 200 micrograms (1000 IU) and 330 micrograms (1650 IU) and should be given to the mother as soon as possible after delivery, at the latest within 72 hours.

lf a large feto-maternal hemorrhage is suspected, its extent should be determined by a suitable method and additional doses of anti-D should be administered as indicated.

Antepartum and postpartum prophylaxis:
200-330 micrograms (1000-1650 IU) in week 28 and 34 of pregnancy; in certain cases, earlier initiation of prophylaxis is possible if medically justified.
If the newborn is Rh(D) positive, a further dose of 200-330 micrograms (1000-1650 IU) should be administered to the mother within 72 hours after delivery.

Ectopic pregnancy, hydatic mole, abortion:
Before week 12 of pregnancy:
120-150 micrograms (600-750 IU) is recommended within 72 hours after the event.
After week 12 of pregnancy:
250-330 micrograms (1250-1650 IU) are recommended within 72 hours after the event.

Amniocentesis, chorionic biopsy:
250-330 micrograms (1250-1650 IU) are recommended within 72 hours after the event.

Macrotransfusion:
10-25 micrograms (50-125 IU) per ml of infiltrated fetal Rh(D) positive erythrocytes.

Rh(D) incompatible blood or erythrocyte transfusion:
In case of a whole blood transfusion, the volume of Rh(D) positive whole blood administered is multiplied by the hematocrit of the donor unit giving the volume of red blood cells transfused. For every 10 ml of Rh(D) positive red blood cells transfused, the patient should receive a single dose of 250 micrograms (1250 IU), but within 72 hours after the event.
Treatment should be given (without preceding exchange transfusion) only if the transfused Rh(D) positive blood represents less than 20% of the circulating red cells.

Method of administration

PARTOBULIN SDF is to be administered slowly by deep intramuscular injection.

In case of hemorrhagic disorders where intramuscular injections are contraindicated, PARTOBULIN SDF may be administered subcutaneously. Careful manual pressure with a compress should be applied to the site after injection.

If large total doses (> 5 ml) are required, it is advisable to administer them in divided doses at different sites, but within 72 hours after the event.

4.3 Contraindications

Hypersensitivity to any of the components.
The product is not intended for use in Rh(D) positive individuals.

4.4 Special warnings and special precautions for use

Special precautions

The product must not be given intravenously (risk of shock).

In the case of postpartum use, the product is intended for maternal administration. It should not be given to the newborn infant.

Patients should be observed for at least 20 minutes after administration of PARTOBULIN SDF.

If hypersensitivity reactions occur during administration of PARTOBULIN SDF, the injection should be stopped immediately.

True hypersensitivity reactions are rare but allergic type responses to Anti-D immunoglobulins may occur. Patients should be informed of signs of hypersensitivity reactions including hives, generalized urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis. The treatment required depends on the nature and severity of the side effect. Minor reactions may be controlled by antihistamines. In case of shock, the current medical standards for shock treatment are to be observed.

PARTOBULIN SDF contains a small quantity of IgA. Although anti-D immunoglobulin has been used successfully to treat selected IgA deficient individuals, the attending physician must weigh the benefit against the potential risks of hypersensitivity reactions. Individuals deficient in IgA have a potential for development of IgA antibodies and anaphylactic reactions after administration of blood components containing IgA.

Patients with incompatible transfusion, who receive anti-D immunoglobulin, should be monitored clinically and by biological parameters, because of the risk of hemolytic reaction.

Special warnings

When medicinal products prepared from human blood or plasma are administered, infectious diseases due to transmission of infective agents cannot be totally excluded. This also applies to pathogens of unknown nature. The risk of transmission of infective agents is however reduced by:

- selection of donors by a medical interview and screening of individual donations and plasma pools for HbsAg and antibodies to HIV and HCV.
- testing of plasma pools for genomic material of HCV.
- virus inactivation/removal procedures included in the production process that have been validated using target and/or model viruses. These procedures are considered effective for HIV-1 and -2, HCV, HAV, and parvovirus B19.

It is strongly recommended that, every time that PARTOBULIN SDF is administered to patients, the name and batch number of the product are recorded.

4.5 Interactions with other medicinal products and other forms of interactions

Active immunization with live virus vaccines (e.g. measles, mumps or rubella) should be postponed until 3 months after the last administration of anti-D immunoglobulin, as the efficacy of the live virus vaccine may be impaired. lf anti-D immunoglobulin needs to be administered within 2-4 weeks of a live virus vaccination, then the efficacy of such a vaccination may be impaired.

After injection of immunoglobulin the transitory rise of the various passively transferred antibodies in the patients blood may result in misleading positive results in serological testing.

The results of blood typing and antibody testing including the Coombs or antiglobulin test, are significantly affected by the administration of anti-D immunoglobulin.

4.6 Pregnancy and lactation

Anti-D immunoglobulin has been used in pregnant women for many years. No harmful effects on the course of pregnancy, the fetus, or the neonate are known.

4.7 Effects on ability to drive and use machines

No effects on ability to drive and use machines have been observed.

4.8 Undesirable effects

Local pain or tenderness may occur at the injection site. To a large extent, this can be prevented by dividing higher doses (> 5 ml) over several injection sites.

Occasionally fever, malaise, headache, cutaneous reactions and chills occur. In rare cases: nausea, vomiting, hypotension, tachycardia, and allergic or anaphylactic type reactions, including dyspnoea and shock, are reported, even when the patient has shown no hypersensitivity to previous administration.

For information on viral safety see 4.4.

4.9 Overdose

No data are available on overdosage. Patients with incompatible transfusion who receive an overdose of anti-D immunoglobulin, should be monitored clinically and by biological parameters, because of the risk of hemolytic reaction.
In other Rh(D)-negative individuals overdosage should not lead to more frequent or more severe undesirable effects than the normal dose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immune sera and immunoglobulins: Anti-D (Rh) immunoglobulin. ATC code: J06BB01.
Anti-D immunoglobulin contains specific antibodies (IgG) against the D (Rh_0) antigen of human erythrocytes.

5.2 Pharmacokinetic properties

Measurable levels of antibodies are obtained at least 24 hours after intramuscular injection. Peak serum levels are usually achieved 2 to 3 days after administration.

The half-life in the circulation of individuals with normal IgG levels is 3 to 4 weeks.

IgG and IgG-complexes are broken down in cells of the reticuloendothelial system.

5.3 Preclinical safety data

Single dose toxicity studies demonstrate that the doses several times higher than the recommended human dosage had no toxic effects on laboratory animals.

Repeated dose toxicity testing in animals is impracticable due to interference with developing antibodies to heterologous protein.

Since human proteins are not seen to cause tumorigenic or mutagenic effects, experimental studies particularly in heterologous species are not considered necessary.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polyethylene Glycol
Glycine
Sodium Chloride

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products and is to be administered as a separate injection.

6.3 Shelf-life

Two years when stored between +2°C and +8°C.
PARTOBULIN SDF must not be used beyond the expiry date indicated on the label.

6.4 Special precautions for storage

Protect from light.
Do not freeze.
Store out of reach and sight of children.

6.5 Nature and contents of container

PARTOBULIN SDF is supplied in preloaded syringes containing single doses of 1 ml (250 micrograms = 1250 IU).

6.6 Instructions for use and handling and disposal

The product should be brought to room or body temperature before use.

Usually the solution is clear or slightly opalescent. Do not use solutions that are turbid or have deposits.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Baxter Healthcare Ltd.
Caxton Way
Thetford
Norfolk
IP24 3SE

8. MARKETING AUTHORISATION NUMBER

PL 0116/0407

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

October 2003

10. DATE OF REVISION OF THE TEXT

October 2003

Annex 2

SUMMARY OF PRODUCT CHARACTERISTCIS

1. Name of the Medicinal Product

D-GAM ®, Human Anti-D Immunoglobulin

2. Qualitative and Quantitative Composition

Human Anti-D Immunoglobulin Ph.Eur.*
Each vial contains: 5 - 50 mg/L protein (250 and 500 iu vials) or 20 - 180 mg/L protein (1,500 and 2,500 iu vials) of which at least 95% is gammaglobulin (IgG). The product contains less than 0.02% w/w of IgA. For excipients see 6.1. The product is prepared from plasma from RhD-negative screened donors who have been immunised against RhD antigen and contains specific antibodies against erythrocyte RhD antigen. Donors are selected from the USA.

* The product is presented in three different concentrations but the highest concentration is filled in different volumes to achieve two dose presentations. The product is therefore available in four nominal doses, namely 250 iu per vial, 500 iu per vial, 1,500 iu per vial and 2,500 iu per vial.

3. Pharmaceutical Form

A solution for injection.

4. Clinical Particulars

4.1 Therapeutic indications

Prevention of RhD immunisation in RhD negative women:

i. Pregnancy/delivery of a RhD positive baby.
ii. Abortion/threatened abortion, ectopic pregnancy or hydatidiform mole.
iii. After ante-partum haemorrhage (APH), amniocentesis, chorionic biopsy or obstetric manipulative procedure e.g. external version, or abdominal trauma, which may cause transplacental haemorrhage (TPH).

Treatment of RhD negative patients after incompatible transfusions of RhD positive blood or other products containing red blood cells (e.g. platelets).

4.2 Posology and method of administration

Posology

a) Post-Natal Dosage:
The recommended dose is 500 iu.
For postnatal use, the product should be administered as soon as possible within 72 hours of delivery.
If a large fetomaternal haemorrhage is suspected, its extent should be determined by a suitable method and additional doses of anti-D should be administered as indicated.

b) Ante-Natal Prophylaxis:
500 iu given at both 28 and 34 weeks of gestation.

c) Following a Potentially Sensitising Event During Pregnancy:
D-GAM ® should be administered as soon as possible and no later than 72 hours after the event.
Up to 20 weeks gestation: recommended dose is 250 iu per incident.
After 20 weeks gestation: recommended dose is 500 iu per incident. A test for the size of the FMH should be performed when anti-D is given after 20 weeks and additional doses of anti-D should be administered as indicated.

d) Prevention of Immunisation in RhD Negative Patients Given Blood Components Containing RhD Positive Cells:
Recommended doses: 125 iu per ml of transfused RhD positive red cells; 250 iu per three adult doses of platelets.

Method of administration

For intramuscular use (preferably into the deltoid muscle).
D-GAM ® is for single injection only.
In the case of haemorrhagic disorders, where intramuscular injections are contra-indicated, Anti-D immunoglobulin may be administered subcutaneously. Careful manual pressure with a compress should be applied to the site after injection.
If large total doses (□5 ml) are required, it is advisable to administer them in divided doses at different sites.

4.3 Contraindications

Hypersensitivity to any of the components.

4.4 Special warnings and precautions for use

Do not administer this product intravenously (risk of shock).
In the case of post-partum use, the product is intended for maternal administration. It should not be given to the newborn infant.
The product is not intended for use in RhD positive individuals.
Patients should be observed for at least 20 minutes after administration.
If symptoms of allergic or anaphylactic type reactions occur, immediate discontinuation of the administration is required.
True hypersensitivity reactions are rare but allergic type responses to Anti-D immunoglobulin may occur. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis. The treatment required depends on the nature and severity of the side effect. In case of shock, the current medical standards for shock treatment should be observed.
D-GAM ® contains a small quantity of IgA. Although anti-D immunoglobulin has been used successfully to treat selected IgA deficient individuals, the attending physician must weigh the benefit against the potential risks of hypersensitivity reactions. Individuals deficient in IgA have a potential for development of IgA antibodies and anaphylactic reactions after administration of blood components containing IgA.
When medicinal products prepared from human blood or plasma are administered, infectious diseases due to transmission of infective agents cannot be totally excluded. This also applies to pathogens of hitherto unknown nature. The risk of transmission of infective agents is however reduced by:

(i) Selection of donors by a medical interview and screening of individual donations and plasma pools for HBsAg and antibodies to HIV and HCV.
(ii) Testing of plasma pools for HCV genomic material.
(iii) Inactivation/removal procedures included in the production process that have been validated using model viruses. These procedures are considered effective for HIV, HCV and HBV. The specific virus inactivation process used is solvent/detergent treatment.

The viral removal/inactivation procedures may be of limited value against non-enveloped viruses such as hepatitis A virus or parvovirus B19.
In the interest of patients, it is recommended that, whenever possible, every time that D-GAM ® is administered to them, the name and batch number of the product is registered.

4.5 Interaction with other medicinal products and other forms of interaction

Active immunisation with live virus vaccines (e.g. measles, mumps or rubella) should be postponed until 3 months after the administration of Anti-D immunoglobulin, as the efficacy of the live virus vaccine may be impaired. If Anti-D immunoglobulin needs to be administered within 2-4 weeks of a live virus vaccination, then the efficacy of such a vaccination may be impaired.
After injection of immunoglobulin, the transitory rise of the various passively transferred antibodies in the patient's blood may result in misleading positive results in serological testing.
The results of blood typing and antibody testing, including the Coombs' or antiglobulin test, are significantly affected by the administration of anti-D immunoglobulin.

4.6 Pregnancy and lactation

This medicinal product is used in pregnancy.

4.7 Effects on ability to drive and use machines

No effects on ability to drive and use machines have been observed.

4.8 Undesirable effects

Local pain and tenderness can be observed at the injection site; this can be prevented by dividing larger doses over several injection sites.
Occasionally fever, malaise, headache, cutaneous reactions and chills occur. In rare cases: nausea, vomiting, hypotension, tachycardia and allergic or anaphylactic type reactions, including dyspnoea and shock, are reported, even when the patient has shown no hypersensitivity to previous administration.
For information on viral safety see 4.4.

4.9 Overdose

No data are available on overdosage. Patients with incompatible transfusion who receive a large dose of anti-D immunoglobulin should be monitored clinically and by biological parameters, because of the risk of haemolytic reaction.
In other RhD negative individuals, overdosage should not lead to more frequent or more severe undesirable effects than the normal dose.

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immune sera and immunoglobulins: Anti-D (Rh) immunoglobulin. ATC code: J06B B01.
Anti-D immunoglobulin contains specific antibodies (IgG) against the RhD antigen of human erythrocytes.

5.2 Pharmacokinetic properties

Measurable levels of antibodies are obtained approximately 8 hours after intramuscular injection. Peak serum levels are usually achieved 2 to 3 days later.
The half-life in the circulation of individuals with normal IgG levels is 3 to 4 weeks.
IgG and IgG-complexes are broken down in cells of the reticuloendothelial system.

5.3 Preclinical safety data

D-GAM ® is a preparation of human plasma proteins, so safety testing in animals is not particularly relevant to the safety of use in man. Acute toxicity studies in rat and mouse showed species specific reactions, which bear no relevance to administration in humans.
Repeated dose safety testing is impracticable due to the induction of and interference with antibodies to human protein. Clinical experience provides no sign of tumourigenic and mutagenic effects.

6. Pharmaceutical Particulars

6.1 List of excipients

Sodium chloride
Glycine
Sodium acetate trihydrate
Sodium hydroxide

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Stored at 2°- 8°C:	2 years.
Stored at 25°C:	1 week.

6.4 Special precautions for storage

D-GAM ® should be stored in the original container at 2°C to 8°C. Storage for up to one week at ambient temperatures (25°C) in the original container is not detrimental. DO NOT FREEZE.
The condition of date-expired, or incorrectly stored product cannot be guaranteed. Such product may be unsafe, and should not be used.

6.5 Nature and contents of container

Neutral borosilicate glass vial (Type I Ph.Eur.) with overseal consisting of a halobutyl rubber wad (Type I Ph.Eur.), clear lacquered aluminium skirt and flip-off polypropylene cap.

6.6 Instructions for use, handling and disposal

The product should be brought to room or body temperature before use.
The solution should be clear or slightly opalescent. Do not use solutions which are cloudy or have deposits.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorisation Holder

Bio Products Laboratory
Dagger Lane
Elstree
Hertfordshire
WD6 3BX
United Kingdom

8. Marketing Authorisation Number(s)

MA049/00801

9. Date of First Authorisation/Renewal of the Authorisation

28th January 2008

10. Date of Revision of the Text