



HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

20 October 2010

RHESONATIV 625 IU/ml, solution for injection, 1-ml vial
B/1 (CIP code: 399 836 4)
RHESONATIV 625 IU/ml, solution for injection, 2-ml vial
B/1 (CIP code: 399 837 0)
B/10 (CIP code: 399 838 7)

Applicant : OCTAPHARMA FRANCE

human anti-D immunoglobulin
ATC code: J06BB01

List I

Date of Marketing Authorisation (by mutual recognition): 02.04.10

Reason for request: Inclusion on the list of medicines approved for hospital use.

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Human anti-D immunoglobulin

1 ml contains:

Human anti-D immunoglobulin.....625 IU (125 µg)

1.2. Therapeutic indications

“Prevention of RhD immunisation in RhD-negative women”

- Antenatal prophylaxis
 - Planned antenatal prophylaxis
 - Antenatal prophylaxis following various complications of pregnancy, including miscarriage/risk of miscarriage, extra-uterine pregnancy or hydatidiform mole, intrauterine foetal death (IUFD), transplacental haemorrhage (TPH) following antepartum haemorrhage (APH), amniocentesis, chorionic biopsy or obstetric procedures such as external version, invasive procedures, cordocentesis, sudden abdominal trauma or foetal therapeutic procedure.
- Post-natal prophylaxis
 - Delivery of an RhD-positive baby (D, weak D, partial D)

Treatment of RhD-negative individuals who have had an incompatible transfusion of RhD-positive blood or other products containing red blood cells, such as platelet concentrates.”

1.3. Dosage (see SPC)

Prevention of RhD immunisation in RhD-negative women

- Antenatal prophylaxis: the current doses according to general guidelines range from 50 to 330 µg, i.e. 250 to 1,650 IU.

- Planned antenatal prophylaxis:

A single dose (e.g. 250 µg or 1,250 IU) between weeks 28 and 30 of pregnancy, or two doses in week 28 and 34.

- Antenatal prophylaxis following complications of pregnancy:

A single dose (e.g. 125 µg or 625 IU before week 12 of pregnancy and 250 µg or 1,250 IU after week 12 of pregnancy) must be administered as soon as possible within 72 hours, and repeated if necessary at 6- to 12-week intervals throughout pregnancy.

A single dose (e.g. 250 µg or 1,250 IU) must be administered after amniocentesis or chorionic biopsy.

- Post-natal prophylaxis: the current doses according to general guidelines range from 100 to 300 µg, i.e. 500 to 1,500 IU.

Standard dose: 1,250 IU (250 µg).

For post-natal administration, the product must be given to the mother as soon as possible within 72 hours after delivery of an Rh-positive child (D, weak D, partial D).

The post-natal dose must be administered even if antenatal prophylaxis has been given and even if analysis of the mother's serum shows residual activity of the antenatal prophylaxis.

If significant foeto-maternal haemorrhage (> 4 ml, 0.7% to 0.8% of women) is suspected, the severity of haemorrhage must be determined by a suitable method (Kleihauer-Betke acid elution test or flow cytometry test) and additional doses of anti-D immunoglobulin must be given according to the findings (10 µg or 50 IU per 0.5 ml of foetal red blood cells).

Incompatible red blood cell (RBC) transfusions

The recommended dose is 20 µg (100 IU) anti-D immunoglobulin per 2 ml of RhD-positive blood or 1 ml of red blood cell concentrate received in transfusion. The appropriate dose must be decided in consultation with a blood transfusion specialist. Tests to monitor RhD-

positive red blood cell levels must be carried out every 48 hours, and anti-D immunoglobulins must be re-administered until all RhD-positive red blood cells have been eliminated from the bloodstream. A maximum dose of 3,000 µg (15000 IU) is sufficient in the event of major incompatible transfusions (> 300 ml of RhD-positive red blood cells).

An alternative intravenous solution is recommended to ensure that adequate plasma levels are immediately obtained. If no intravenous solution is available, a high dose should be administered by the intramuscular route, splitting the dose over a period of several days.

Methods of administration

RHESONATIV 625 IU/ml must be administered by intramuscular injection.

If high overall doses (>2 ml for children or >5 ml for adults) are necessary, practitioners are advised to split the total dose between various injection sites.

Patients with haemorrhagic disorders which mean that intramuscular injection is contraindicated can receive RHESONATIV 625 IU/ml by subcutaneous injection if no intravenous injection solution is available. Slight pressure must be exerted on the site following the injection, using a compress.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2010)

J : Antiseptics for systemic use
J06 : Immune sera and immunoglobulins
J06B : Immunoglobulins
J06BB : Specific immunoglobulins
J06BB01 : Anti-D (Rh) immunoglobulins

2.2. Medicines in the same therapeutic category

A human anti-D immunoglobulin is currently available in France in two dosages:

RHOPHYLAC 200 µg/2 ml, solution for injection in prefilled syringe

RHOPHYLAC 300 µg/2 ml, solution for injection in prefilled syringe

RHOPHYLAC can be administered by intravenous or intramuscular injection.

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The dossier submitted by the pharmaceutical firm is based on old bibliographic data:

- Seven studies on the prevention of RhD immunisation in RhD-negative women;
- One study on RhD-incompatible blood transfusion;
- One pharmacokinetic study¹ which will not be described in this document.

3.1.1. In the indication “prevention of RhD immunisation in RhD-negative women”

The dossier includes seven studies on the prevention of RhD immunisation in RhD-negative women (see table 1);

- Five studies assessing the efficacy and tolerance of RHESONATIV 625 IU/ml as post-partum prophylaxis in the 72 hours following delivery;
- Two studies assessing the efficacy and tolerance of RHESONATIV 625 IU/ml as antenatal prophylaxis combined with post-partum prophylaxis;

Treatment was over 99% effective in preventing RhD immunisation in the various studies: RhD immunisation rates ranged from 0% to 0.7% for post-partum prophylaxis and from 0% to 0.4% in antenatal prophylaxis.

Table 1: studies on the prevention of RhD immunisation in RhD-negative women

Study	Study methodology	Indication*	Number of subjects	Rh status of mother / child	Duration of follow-up	Incidence of anti-D antibodies %
Orjasaeter et al., 1972 ²	Open-label study	PPP	1,937	negative/positive	6 months	0.4
Eklund et al., 1978 ³	Open-label study	PPP	38,123	negative/positive	4-6 months	0.1
			8,688	negative/positive	next delivery	0.7
Bartsch et al., 1972 ⁴	Open-label study	PPP	917	negative/positive	6 months	0.3
Dambrioso et al., 1971	Open-label study	PPP	665	negative/positive	6 months	0.2
Hermann et al., 1976 ⁵	Open-label study	PPP	608	negative/positive	6-8 months	0.3
		ANP [‡] + PPP	103	negative/positive	8 months	0
Selbing et al.	Open-label study	PPP	475	negative/positive	not reported	0
Herman et al., 1984 ⁶	Open-label study	ANP [‡] + PPP	529	negative/positive	8 months	0.4

* PPP: post-partum prophylaxis; ANP: antenatal prophylaxis

‡ 6-8 weeks before the expected delivery date

¹ Eklund J, Hermann M, Kjellman H, et al: Turnover rate of anti-D IgG injected during pregnancy. Br.Med.J.(Clin.Res.Ed) 1982; 284:854-855

² Orjasaeter H. Rh-antibodies in women receiving preventive treatment against Rh-immunization. Experiences after 2 years preventive program]. Tidsskr.Nor Laegeforen. 1972; 92:2412-2414

³ Eklund J. Prevention of Rh immunization in Finland. A national study, 1969--1977. Acta Paediatr.Scand.Suppl 1978; 1-57

⁴ Bartsch FK. Foetal erythrocytes in maternal blood and immunoprophylaxis of Rh-immunization. Clinical and experimental studies. Acta Obstet.Gynecol.Scand.Suppl 1972; 20:1-128

⁵ Hermann M. Rh-prophylaxis with immunoglobulin anti-D administrated during and after delivery. Acta Obstet.Gynecol.Scand.Suppl 1976; 49:1

⁶ Hermann M. Antenatal prophylaxis of Rh immunization with 250 micrograms anti-D immunoglobulin. Acta Obstet.Gynecol.Scand.Suppl 1984; 124:1-15

3.1.2. In the indication “treatment of RhD-negative individuals who have had an incompatible transfusion of RhD-positive blood or other products containing red blood cells, such as platelet concentrates, prevention of RhD immunisation in RhD-negative women.”

The dossier contains one study assessing the efficacy of RHESONATIV 625 IU/ml in 21 RhD-negative volunteers (Bartsch et al., 1972)⁷.

The subjects received an injection of foetal RhD-positive red blood cells in quantities corresponding to

- 10 ml of cord blood (n = 1)
- 25 ml (n= 10)
- 50 ml (n= 10).

After 48 to 72 hours, 260 µg of RHESONATIV 625 IU/ml were administered by intramuscular injection.

No serological evidence of RhD immunisation was detected in the subjects six months (nine months in one case) after the start of the study.

Six months to two and a half years later, eight subjects in the 25-ml group and the 10 subjects in the 50-ml group were given 5 ml of RhD-positive cord blood. Doses of 260 and 333 µg of RHESONATIV 625 IU/ml respectively were injected after 48 to 72 hours. No RhD antibodies were detected in any of the volunteers after a further period of 6 months (8 months in one case).

3.2. Adverse effects

- The uncommon ($\geq 1/1,000$, $< 1/100$) adverse effects referred to in the SPC for RHESONATIV 625 IU/ml are : headache, general disorders and reactions at the injection site. Allergic or anaphylactic reactions can appear in rare cases;
- The last PSUR, covering the period from 1 September 2006 to 31 August 2009 (485 million IU sold in 48 countries)⁸, contained two reports of adverse effects, one of which was regarded as serious (suspected transmission of an infectious agent (a non-specified hepatitis virus)).

3.3. Conclusion

Old bibliographical data (studies published between 1971 and 1984) have shown RHESONATIV 625 IU/ml given by intramuscular injection to be effective in preventing RhD immunisation in RhD-negative subjects.

This efficacy was shown in particular in RhD-negative pregnant women. It was found in the various studies to be over 99% effective, producing an RhD immunisation rate of 0% to 0.7% when administered as post-partum prophylaxis and 0% to 0.4% when given as antenatal prophylaxis.

RHESONATIV 625 IU/ml is well tolerated, except for rare cases of allergic reaction to human anti-D immunoglobulins.

⁷ Bartsch FK. Foetal erythrocytes in maternal blood and immunoprophylaxis of Rh-immunization. Clinical and experimental studies. Acta Obstet.Gynecol.Scand.Suppl 1972; 20:1-128

⁸ Based on the recommended dose for the principal indication (post-partum prophylaxis) of 1,250 IU given in a single dose, the number of patients treated during this period is estimated at around 388,000

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

In RhD-negative women, RhD immunisation can lead to haemolysis, severe foetal and neonatal anaemia, and severe neonatal jaundice.

Incompatible transfusion of RhD-positive blood or other products containing RhD-positive red blood cells leads to severe, acute haemolysis.

RHESONATIV 625 IU/ml is a human anti-D immunoglobulin indicated in the prevention of RhD immunisation in RhD-negative women during pregnancy and childbirth, and in the treatment of RhD-negative individuals following incompatible transfusions of RhD-positive blood or other products containing red blood cells.

The efficacy/adverse effects ratio of this medicinal product is high.

RHESONATIV 625 IU/ml must be administered by intramuscular injection. There is an alternative treatment which can be administered by intramuscular or intravenous injection (RHOPHYLAC).

RHESONATIV 625 IU/ml is a first-line treatment for the prevention of RhD immunisation. However, it is not suitable for the following situations:

- Because of its pharmaceutical form, as planned antenatal prophylaxis for RhD-negative women. The French guidelines recommend systematic prophylaxis at 28 weeks amenorrhoea (+/- 1 week) in the form of a single injection of 1,500 IU (300 µg) anti-D immunoglobulin for all RhD-negative women who have not been immunised against the D antigen (CNGOF, 2005)⁹. The strongest form of RHESONATIV 625 IU/ml contains only 1,250 IU (250 µg);
- Because it is administered by the intramuscular route:
 - o as antenatal prophylaxis for RhD-negative women following complications in the second or third trimester of pregnancy (see details in appendix 1) with an established foetomaternal haemorrhage (positive Kleihauer test result). In this situation, preference must be given to intravenous administration of an anti-D immunoglobulin⁹;
 - o as post-natal prophylaxis for RhD-negative women who have given birth to an RhD-positive baby with established foetomaternal haemorrhage (positive Kleihauer test result). In this situation, preference must be given to intravenous administration of an anti-D immunoglobulin⁹;
 - o in the treatment of RhD-negative individuals who have had an incompatible transfusion of RhD positive blood or other products containing red blood cells, such as platelet concentrates. In this situation, intravenous administration of an anti-D immunoglobulin is recommended in order to obtain adequate plasma levels without delay (see SPC).

Public health benefit

The public health burden represented by neonatal haemolytic disorders following alloimmunisation is low, as post-natal prophylaxis means that the number of infants affected is low.

However, there is a very small residual risk of alloimmunisation linked to silent foetomaternal haemorrhage in the third trimester of pregnancy. In addition, the

⁹ Prevention of foetomaternal Rhesus D alloimmunisation: Guidelines for clinical practice developed by the French National Association of Gynaecologists and Obstetricians. *Gynécologie Obstétrique & fertilité* 2006; 34(4):360-365

expected reduction in morbidity and mortality following the use of antenatal prophylaxis is small, amounting to around 500 additional protected pregnancies a year.

There is no public health need, and the therapeutic need is already covered as another anti-D immunoglobulin treatment (RHOPHYLAC) is already available. This alternative treatment is suitable for all clinical situations requiring the use of anti-D immunoglobulins (as it can be administered by intravenous injection and is available in different dose levels).

In addition, the data available does not indicate that RHESONATIV 625 IU/ml would have any impact on the morbidity and mortality associated with this pathology.

Moreover, it is not feasible to screen foetuses for RhD-positive status because the methods available are invasive, and administering antenatal prophylaxis to a woman carrying an RhD-negative foetus would also expose women to the treatment who would not benefit from it.

Consequently, the proprietary medicinal product RHESONATIV 625 IU/ml is not expected to have any public health impact for any of its indications.

In conclusion:

The actual benefit of RHESONATIV 625 IU/ml is substantial in the following situations:

- Prevention of RhD immunisation in RhD-negative women:
 - o as antenatal prophylaxis where a risk factor for foetomaternal haemorrhage in the first trimester of pregnancy is present;
 - o as antenatal prophylaxis where a risk factor for foetomaternal haemorrhage is present in the second or third trimester of pregnancy when the Kleihauer test result is negative;
 - o as post-natal prophylaxis after delivery of an RhD-positive baby when the Kleihauer test result is negative.

In view of the fact that the product can only be given by intramuscular injection and in the light of the dose levels available, **the actual benefit of RHESONATIV 625 IU/ml is insufficient in the following situations:**

- Prevention of RhD immunisation in RhD-negative women:
 - o as planned antenatal prophylaxis in the third trimester of pregnancy;
 - o as antenatal prophylaxis following complications of pregnancy in the second or third trimester with established foetomaternal haemorrhage (Kleihauer test result positive);
 - o as post-natal prophylaxis after delivery of an RhD-positive baby with established foetomaternal haemorrhage (Kleihauer test result positive);
- In the treatment of RhD-negative individuals who have had an incompatible transfusion of RhD positive blood or other products containing red blood cells, such as platelet concentrates.

4.2. Improvement in actual benefit (IAB)

RHESONATIV 625 IU/ml provides no improvement in actual benefit (IAB V) compared to RHOPHYLAC.

4.3. Therapeutic use

Apart from rare cases of transfusion accidents, RhD immunisation is caused by the synthesis of anti-D IgG antibodies in RhD-negative women in response to the transplacental transfer of RhD-positive foetal erythrocytes during an obstetric event (delivery, miscarriage, abortion, extra-uterine pregnancy, invasive antenatal diagnostic procedure, etc.). RhD immunisation causes severe foetal and neonatal anaemia and severe neonatal jaundice.

The injection of human anti-D immunoglobulins as prophylaxis before and after delivery plays a vital role in preventing RhD immunisation in RhD-negative women.

The current recommendations in France⁹ are:

- If a risk factor for foetomaternal haemorrhage during pregnancy (see appendix 1) is present: and injection of 100 to 200 µg (500 to 1,000 IU) of anti-D immunoglobulin is recommended in the first trimester and from the second trimester onwards. The dose needs to be set according to the results of a foetomaternal haemorrhage quantification test (Kleihauer test);
- In the third trimester of pregnancy: an injection of 300 µg (1,500 IU) of anti-D immunoglobulins by intramuscular injection must be offered at 28 weeks amenorrhoea (+/- 1 week) to all RhD-negative pregnant women who have not been immunised against the D antigen and whose foetus is known or assumed to be RhD-positive.
- At the time of delivery: if the infant is RhD-positive, the dose and method of administration are adjusted in the light of the Kleihauer test result. If the Kleihauer test result is positive, the direct intravenous or perfusion administration routes are recommended.

Place of RHESONATIV 625 IU/ml (see appendix 2)

RHESONATIV 625 IU/ml administered by intramuscular injection is suitable for preventing RhD immunisation in RhD-negative women:

- as antenatal prophylaxis where a risk factor is present in the first trimester of pregnancy;
- as antenatal prophylaxis where a risk factor is present in the second or third trimester of pregnancy when the Kleihauer test result is negative;
- as post-natal prophylaxis after delivery of an RhD-positive baby when the Kleihauer test result is negative.

The intravenous route is strongly recommended if significant foetomaternal haemorrhage has been established, or when the 72-hour deadline for administration after a potentially immunising event is close⁹.

Under these circumstances, preference must be given to direct intravenous or perfusion administration of RHOPHYLAC.

Preference must be given to intravenous administration of RHOPHYLAC in the case of patients with haemorrhagic disorders which contraindicate intramuscular injection. RHESONATIV 625 IU/ml can be administered via the subcutaneous route if no anti-D immunoglobulin suitable for administration via the intravenous route is available.

The French guidelines for planned antenatal prophylaxis for RhD-negative women recommend systematic prophylaxis in the third trimester of pregnancy based on a single injection of 1,500 IU (300 µg) of anti-D immunoglobulin at 28 weeks amenorrhoea (+/- 1 week)⁹. The strongest pharmaceutical form of RHESONATIV 625 IU/ml contains only 1,250 IU (250 µg).

4.4. Target population

The target population of RHESONATIV 625 IU/ml is defined by the number of RhD-negative women exposed to the risk of RhD immunisation who would benefit from prophylaxis involving injection of anti-D immunoglobulin.

It is thought that around 1,100,000 to 1,200,000 pregnancies are started each year¹⁰. On average, 15%¹⁰ of the French population are RhD-negative, which gives a total number of RhD-negative women becoming pregnant of 165,000 to 180,000 a year.

The likelihood of an RhD-negative woman conceiving an RhD-positive foetus is 60%¹⁰, so the number of RhD-negative women bearing an RhD-positive foetus is estimated at **99,000 to 108,000 a year**.

¹⁰ Branger B., et Winer N. Epidémiologie de l'allo-immunisation anti-D pendant la grossesse [Epidemiology of anti-D alloimmunisation during pregnancy]. J Gynecol Obstet Biol Reprod 2006 ; 35(S1) :1S87-1S92

4.5. Transparency Committee recommendations

The transparency Committee recommends inclusion on the list of medicines approved for hospital use and various public services in the following situations:

- Prevention of RhD immunisation in RhD-negative women:
 - o as antenatal prophylaxis where a risk factor for foetomaternal haemorrhage in the first trimester of pregnancy is present;
 - o as antenatal prophylaxis where a risk factor for foetomaternal haemorrhage is present in the second or third trimester of pregnancy when the Kleihauer test result is negative;
 - o as post-natal prophylaxis after delivery of an RhD-positive baby when the Kleihauer test result is negative.

The transparency Committee does not recommend inclusion on the list of medicines approved for hospital use and various public services in the following situations:

- Prevention of RhD immunisation in RhD-negative women:
 - o as planned antenatal prophylaxis in the third trimester of pregnancy;
 - o as antenatal prophylaxis following complications of pregnancy in the second or third trimester with established foetomaternal haemorrhage (Kleihauer test result positive);
 - o as post-natal prophylaxis after delivery of an RhD-positive baby with established foetomaternal haemorrhage (Kleihauer test result positive);
- In the treatment of RhD-negative individuals who have had an incompatible transfusion of RhD positive blood or other products containing red blood cells, such as platelet concentrates.

Appendix 1: circumstances which may lead to foetomaternal haemorrhage during pregnancy (CNGOF guidelines, 2005)⁹

In the first trimester (moderate risk of foetal red blood cell transfer)

- Any miscarriage or threatened miscarriage in the first trimester
- Abortion at any stage of pregnancy and irrespective of the method used
- Molar pregnancy
- Extra-uterine pregnancy
- Metrorrhagia
- Choriocentesis (chorionic villi biopsy), amniocentesis
- Embryo reduction
- Abdominal trauma
- Cervical cerclage

In the second and third trimesters

Significant risk of foetal red blood cell transfer:

- Abortion on medical grounds
- Late miscarriage
- In-utero foetal death
- External version
- Abdominal or pelvic trauma (at any stage of pregnancy)
- Abdominal or pelvic surgery (at any stage of pregnancy)
- Ovular sample: amniocentesis, cordocentesis, placentocentesis
- Delivery by any method

Moderate risk of foetal red blood cell transfer:

- Metrorrhagia
- Cervical cerclage
- Threat of premature delivery requiring treatment

Appendix 2: suitability of RHESONATIV in the various indications requiring the administration of anti-D immunoglobulins

Indications	Is RHESONATIV suitable?
systematic prophylaxis in the third trimester of pregnancy	+/- (1)
where a risk factor is present in the first trimester of pregnancy	YES
where a risk factor is present in the second or third trimester of pregnancy when the Kleihauer test result is negative	YES
where a risk factor is present in the second or third trimester of pregnancy when the Kleihauer test result is positive	+/- (2)
after delivery of an RhD-positive baby when the Kleihauer test result is negative	YES
after delivery of an RhD-positive baby when the Kleihauer test result is positive	+/- (3)
treatment of RhD-negative individuals who have had an incompatible transfusion of RhD positive blood or other products containing red blood cells, such as platelet concentrates	Usually NO (4)

(1) The French guidelines recommend systematic prophylaxis in the third trimester of pregnancy based on a single injection of 1,500 IU (300 µg) of anti-D immunoglobulins at 28 weeks amenorrhoea (+/- 1 week) for all RhD-negative pregnant women who have not been immunised against the D antigen and whose foetus is known or assumed to be RhD-positive. The strongest form of RHESONATIV 625 IU/ml contains only 1,250 IU (250 µg).

(2) and (3) the intramuscular route is not the most suitable route for the high doses required in this situation (the injections need to be split, which could make the treatment less effective).

(4) the intramuscular route is not suitable for the high doses needed in the event of accidental transfusion of red blood cell concentrates. The intramuscular route is contraindicated for individuals suffering from severe thrombocytopenia or other haemostasis disorders.