RHOPHYLAC® MANUFACTURER'S SUBMISSION
ROUTINE ANTENATAL ANTI-D PROPHYLAXIS FOR Rh D-NEGATIVE WOMEN

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(final version: 17 August 2007)

Submission deadline: 17 August 2007

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Executive summary

Background

The purpose of this review is to provide updated information on the clinical effectiveness, cost-effectiveness and safety of the routine prophylactic use of anti-D immunoglobulin to prevent Rhesus (Rh) isoimmunisation during pregnancy for all Rh-negative women. Since the publication of the 2002 NICE guidelines on routine antenatal anti-D prophylaxis (RAADP) for all non-sensitised pregnant women who are Rh D-negative, a new preparation of anti-D immunoglobulin has been licensed and marketed in the UK (Rhophylac 300 µg or 1500 IU from CSL Behring), and is the subject of this submission. The 2002 guidelines included the only two anti-D immunoglobulin preparations that were then available from Baxter and the Blood Products Laboratory. The latter two products were recommended for use in RAADP in Rh D-negative pregnant women in two doses, one given at 28 weeks, and a second at 34 weeks of pregnancy. Rhophylac is recommended for use in RAADP in a single dose at 28 to 30 weeks of pregnancy. In determining clinical effectiveness of RAADP, the 2002 guidelines acknowledged that two doses of anti-D immunoglobulin were as effective as a one-dose regimen. However, in the absence of a commercially available one-dose regimen in England and Wales, the wording of the 2002 guidelines emphasised a two-dose regimen by default. In support of the two-dose regimen, the 1999 Royal College of Obstetrics and Gynaecology (RCOG) recommendations were cited. This document has now been officially withdrawn (http://www.rcog.org.uk/index.asp?PageID=1972), and replaced with a revised version.

In the intervening period since the publication of the 2002 guidelines, a number of other countries have published their own guidelines on RAADP, which have consistently recommended not the two-dose but the one-dose regimen. Given these changing circumstances, it is now timely and appropriate to submit information relating to single-dose Rhophylac for the prevention of Rh D immunisation in Rh D-negative women. In the UK, Rhophylac is currently approved for RAADP for the prevention of Rh D immunisation in pregnant Rh D-negative women.

Safety and tolerability of Rhophylac

Rhophylac is manufactured from pooled human plasma. The possible risk of transmitting viral infections is minimised at various stages in the manufacturing process including virus inactivation by solvent-detergent treatment, and elimination by nanofiltration. Nanofiltration processes as used for the manufacture of Rhophylac have also been shown to contribute to the removal of abnormal prion protein. There is no evidence in clinical studies of viruses or prions being transmitted through Rhophylac administration.

The safety and tolerability of Rhophylac have been evaluated in six clinical studies, including two unpublished studies. The accumulated data indicate that Rhophylac was safe and generally well tolerated with few adverse events (AEs) being reported. Drug-related AEs were rare and mild, and included pain or itching at the injection site and headache, which have been described for other anti-D products. No anaphylactic or severe allergic reactions were reported.

Clinical effectiveness of Rhophylac

Several studies have shown that Rhophylac rapidly clears Rh D-positive erythrocytes from the circulation in Rh D-negative healthy male volunteers. Rhophylac also provides measurable serum anti-D IgG levels at least nine weeks after administration, with no cases of Rh D sensitisation being reported when administered as a one-dose 1500 IU regimen at 28 week's gestation.

Efficacy of one-dose and two-dose regimens

One study has shown that Rhophylac 1500 IU, when used as a one-dose regimen at 28 weeks' gestation, provides measurable serum anti-D IgG levels at least nine weeks after administration. A further three non-Rhophylac studies have shown that one-dose regimens of RAADP 1500 IU at 28 weeks of gestation are effective in reducing Rh D sensitisation rates, with sensitisation rates ranging from 0.0-0.6% with RAADP, compared with 1.7-1.8% with no RAADP. There have been no published studies directly comparing efficacy between one-dose and two-dose regimens. However, one meta-analysis comparing sensitisation rates between anti-D 1500 IU IgG at 28 weeks' gestation and 500 IU anti-D IgG at 28 and 34 weeks' gestation reported low sensitisation rates with

no significant difference between each regimen (0.34% with the one-dose regimen and 0.30% and 0.35%, respectively, in two separate studies with the two-dose regimen). Compliance rates with the two-dose regimen, although they have improved with increasing experience and education, may still be low. To date, there have been no studies comparing compliance between one-dose and two-dose regimens. In general, implementation of a one-dose regimen may be simpler and is less prone to error than the two-dose regimen.

Current guidelines on RAADP

Current NICE guidelines recommend antenatal prophylaxis at 28 and 34 weeks of gestation (National Institute for Clinical Excellence 2002). The document acknowledges that two doses of anti-D immunoglobulin 500 IU at 28 and 34 weeks into pregnancy appear to be as effective as one 1500 IU dose at 28 weeks, but does not include the single-dose regimen in the recommendations. The British Committee for Standardisation in Haematology recommend a single dose of 1500 IU anti-D IgG at 28 weeks (BCSH 2006). Outside of the UK, one-dose RAADP regimens are recommended in the United States, Canada, France, Switzerland and Germany.

Cost-effectiveness

It is well established that RAADP is a cost-effective intervention for haemolytic disease of the newborn in pregnant women who are Rh D-negative. Two studies have reported that one-dose RAADP regimens are more cost-effective than two-dose regimens.

Conclusions

While it is clear that RAADP is effective in preventing haemolytic disease of the newborn, clinical efficacy data shows no difference in sensitisation rates between one-dose and two-dose regimens. However, there is evidence suggesting that compliance with the two-dose regimen is low and that the one-dose regimen may be more cost-effective. Implementation of a one-dose RAADP regimen may be simpler, may lead to fewer administration errors, and may be more cost-effective than two-dose RAADP regimens, and we respectfully request that one-dose RAADP with Rhophylac be considered for inclusion in the updated guidelines.

Introduction

Aim

The purpose of this review is to evaluate the clinical effectiveness, cost-effectiveness and safety of the routine antenatal anti-D prophylaxis (RAADP) use of anti-D immunoglobulin to prevent Rhesus (Rh) iso-immunisation during pregnancy for all Rh-negative women.

The document will specifically review data on Rhophylac and additional supporting evidence with respect to the current NICE technology appraisal.

Intervention

Routine antenatal anti-D prophylaxis (RAADP)

Population

Non-sensitised pregnant women who are Rh D-negative

Comparators

- RAADP: different dosing regimens and different methods of administration
- No RAADP

Outcomes

- Sensitisation rates of Rh D-negative women (allo-immunisation)
- Rh D-positive erythrocyte clearance rate
- Serum anti-D IgG levels
- Adverse events

Background

Recommendations for the use of anti-D immunoglobulin for anti-D prophylaxis were first issued by a joint working group of the British Blood Transfusion Society and the Royal College of Obstetricians and Gynaecologists in 1999 (Joint Working Group of the British Blood Transfusion Society and the RCOG. 1999). The 1999 document has since been officially withdrawn and interested parties should refer to the 2002 NICE guidelines mentioned below.

In 2002, NICE recommended that routine antenatal anti-D prophylaxis (RAADP) be offered to all non-sensitised pregnant women who are Rh D-negative (National Institute for Clinical Excellence 2002). These guidelines recommend RAADP for all non-sensitised Rh D-negative women at 28 and 34 weeks gestation (a two-dose regimen)(National Institute for Clinical Excellence 2002). The guidelines also stated that two doses of anti-D immunoglobulin at 28 and 34 weeks were found to be as effective as one dose at 28 weeks.

RAADP and the options available should be discussed with the patient so that they can make an informed choice about treatment. The difference between RAADP and prophylactic anti-D given because of likely sensitisation should also be clearly explained to the patient.

Description of Rhophylac®

Brand name: Rhophylac®

Approved name: Rh_0 (D) Immune Globulin Intravenous (Human)

Therapeutic class: Immune sera and immunoglobulins: Anti-D (Rhesus)

Recommended dose for RAADP: A single dose of 1500 IU administered by intravenous or intramuscular injection at 28 to 30 weeks' gestation.

Each pre-filled syringe contains human anti-D immunoglobulin at a dose of 1500 IU (300 μg) for intramuscular or intravenous injection.

UK marketing authorisation

UK marketing authorisation number for indications in this submission: PL 15036/0019

Date received: 7 October 2002 (launched May 2003)

Identification of relevant evidence

Evidence relevant to the technology appraisal is listed in Appendix A.

Treatment aim

- Rhophylac is currently approved for the prevention of Rh D immunisation in pregnancy and obstetric conditions in Rh D-negative women, including antepartum and postpartum Rh prophylaxis and Rh prophylaxis in cases of obstetric complications, invasive procedures during pregnancy, or obstetric manipulative procedures

- Incompatible transfusions in Rh D-negative individuals transfused with blood components containing Rh D-positive red blood cells

This document will focus on the use of Rhophylac in the prevention of Rh D immunisation in non-sensitised, pregnant women, who are Rh D-negative.

Rhophylac is approved for administration intravenously or intramuscularly at a single dose of 1500 IU at 28 to 30 weeks of gestation in the prevention of Rh D immunisation in pregnancy and obstetric conditions in Rh D-negative women. Rhophylac is currently used by 71 centres throughout England and Wales (see Appendix B).

Clinical safety and tolerability

Pathogen and prion safety

Rhophylac is manufactured from pooled human plasma obtained from hyperimmunised donors, using a combination of different chromatographic adsorption stages (Stucki et al 1997).

The possible risk of transmitting viral infections is minimised at various stages of the manufacturing process, including: careful donor selection, testing and blood donations for viral markers (HBs antigen, HIV 1+2 antibodies, HCV antibodies). PCR screening for HIV, HBC, HCV, HAV and B 19 virus (formerly called parvovirus B 19), virus

inactivation by solvent-detergent (S-D) treatment, and virus elimination by nanofiltration and by the chromatographic purification process.

Viruses shown to be removed in validation studies include HIV, bovine viral diarrhoea virus (a model of HCV), pseudorabies virus (a model for large enveloped viruses, including herpes viruses) canine parvovirus, minute virus of mice, bovine parvovirus (models for B 19 virus) (Table 2) (Stucki and Kempf 1997). Viruses are eliminated by inactivation during S-D treatment, and removal by nanofiltration using a 15 nm filter (Stucki and Kempf 1997). The chromatographic purification process also contributes to the removal of viruses.

Table 2. Virus elimination and inactivation during the Rhophylac manufacturing process (Stucki and Kempf 1997)

Virus	**HIV**	**BVDV**	**PRV**	**Parvovirus (CPV/MVM)**	**Parvovirus (BPV)**
Genome	RNA	RNA	DNA	DNA	DNA
Envelope	Yes	Yes	Yes	No	No
S-D treatment	≥6.0	≥5.4	≥5.6	NT	NT
Chromatographic process steps	4.5	1.6	≥3.9	2.5	NT
Nanofiltration	≥6.3	≥5.5	≥5.6	≥3.4	≥5.6
Overall reduction[a]	≥16.8	≥12.5	≥15.1	5.9	≥5.6

[a]Log10 units

HIV, human immunodeficiency virus; BVDV, bovine viral diarrhoea virus (model for Hepatitis C virus); PRV, pseudorabies virus (model for large, enveloped DNA viruses, eg herpes viruses); CPV, canine parvovirus (model for small, non-enveloped DNA viruses); MVM, minute virus of mice (model for small, non-enveloped DNA viruses); BPV, bovine parvovirus (model for human B19 virus); NT, not tested.

Nanofiltration processes as used for the manufacture of Rhophylac have been shown to contribute to the removal of abnormal prion protein (Tateishi et al 2001).

The processes described above, ensure that the possible risk of transmitting viral infections and prions are minimised during the Rhophylac manufacturing process.

Safety and tolerability of Rhophylac

The safety and tolerability of Rhophylac has been evaluated in six clinical studies. In these studies, 628 people were exposed to Rhophylac, 447 (71.2%) of whom were pregnant women. Nine hundred and thirty-one doses of Rhophylac were administered. Rhophylac was safe and generally well tolerated with very few adverse events (AEs) being reported (Table 3). Drug-related AEs were rare and mild, and included pain or itching at the injection site, and headache. These AEs have been described for other anti-D products. No anaphylactic or severe allergic reactions were reported. There was no evidence of viruses being transmitted through Rhophylac administration.

In a pharmacokinetic study of Rhophylac 1500 IU in Rh D-negative pregnant women, a total of seven AEs occurred in five 5/14 (25.7%) patients (Bichler et al 2003). All AEs were mild to moderate in severity and were not considered to be related to study drug. AEs included influenza-like symptoms in 3/14 (21.4%) patients, neuritis in 1/14 (7.14%) and oesophagitis in 1/14 (7.14%).

In a Phase I clinical study of single-dose Rhophylac 1000 IU in Rh D-negative male healthy volunteers no adverse events were reported (Stucki et al 1998). In a second Phase I clinical study of single-dose Rhophylac 1500 IU in Rh D-negative male healthy volunteers, there were 17 AEs in 8/18 (44.4%) subjects; none of the AEs were considered to be severe or serious (CSL Behring UK Ltd 2003). Seven out of eighteen AEs were considered to be possibly related, and 1/18 AEs was considered to be probably related to Rhophylac treatment. The majority of AEs were mild in severity and two were of moderate intensity (flatulence and loose stool in the same subject). The most common AEs were headache in 6/18 (33.3%) subjects, fatigue in 2/18 (11.1%) subjects and general discomfort in 2/18 (11.1%) subjects. There were no withdrawals due to an AE and no deaths. In another Phase I study, no AEs were reported with intravenous or intramuscular single-dose Rhophylac 1500 IU in healthy male volunteers (Miescher et al 2004).

In a Phase II/III clinical study of the post-partum efficacy of single-dose Rhophylac 1000 IU (within 72 hours of delivery) in Rh D-negative women having given birth to a Rh D-positive baby, AEs were rarely reported and none were serious or severe in intensity (CSL Behring UK Ltd 1996). Two cases of rash were observed, which were considered to be possibly related to administration of Rhophylac. In a Phase III clinical study of antenatal (28 weeks' gestation) and postnatal (within 72 hours of delivery) efficacy of single-dose Rhophylac 1500 IU in Rh-negative pregnant women, the majority of AEs were mild in nature and there were no serious AEs (MacKenzie et al 2004). AEs possibly related to treatment included injection site pain in 2/432 (0.46%) patients, mild soreness or itching at the injection site in 2/432 (0.46%) patients, detection of anti-Rh C in serum in 3/432 (0.69%) and polyhydramnios in 1 patient (0.23%).

These data confirm that treatment with Rhophylac is safe and generally well tolerated.

Table 3. Adverse events reported in six clinical studies of Rhophylac (Stucki et al 1998; CSL Behring UK Ltd 2003; CSL Behring UK Ltd 1996; MacKenzie et al 2004; Bichler et al 2003; Miescher et al 2004)

Study	Type of adverse event	Incidence (%)
Study ZLB 621 (Stucki et al 1998)	None reported	0
Study ZLB 00_032 (CSL Behring UK Ltd 2003)	Headache	33.3
	Fatigue	11.1
	General discomfort	11.1
Study ZLB 622 (CSL Behring UK Ltd 1996)	Infection/high fever	0.7
	Tickling cough	0.7
	Rash*	1.4
	Abdominal pain	0.7
Study ZLB 98_011 (MacKenzie et al 2004)	Injection site pain*	0.46
	Mild soreness or itching*	0.46
	Headache*	0.23
	Detection of anti-Rh C in serum*	0.69
	Polyhydramnios*	0.23
Study ZLB 98_012 (Bichler et al 2003)	Influenza-like symptoms	21.42
	Neuritis	7.14
	Oesophagitis	7.14
Miescher et al 2004 (Miescher et al 2004)	No AEs reported	No AEs reported

*Possibly related to Rhophylac administration
AEs, adverse events

Additional safety and tolerability data

One systematic review reported no short-term AEs, such as allergic responses with non-Rhophylac RAADP, in Rh D-negative pregnant women (Chilcott et al 2003). The reported incidence of all AEs was also low. Pharmacovigilance data for one anti-D product in which over 660,000 vials of anti-D were issued, reported only three cases of

AEs possibly or probably-related to RAADP. One AE was related to an anaphylactic reaction. In a similar report for another anti-D product, 2.9 million doses of anti-D were issued and a total of 11 reports of AEs received by the manufacturer. Two of these AEs were serious, although they occurred some time after administration and were thought not to be related to treatment.

Rhophylac was first licensed and launched in Switzerland in 1996. Since 2001, it has been licensed and launched in 23 additional countries, including the UK in 2003. Worldwide, 2.07 million doses have been distributed between initial launch and the end of 2006. A total of 44 suspected adverse drug reaction (ADR) reports relating to Rhophylac and other anti-D products are in the global CSL Behring pharmacovigilance ADR database. Of these, 30 cases are relevant to the safety of Rhophylac. During postmarketing surveillance for RAADP and postpartum administration of Rhophylac, one ADR case per 69000 doses of Rhophylac has been reported. This confirms the excellent safety and tolerability of this product.

These data confirm that RAADP using Rhophylac or other formulations is safe and generally well tolerated.

Clinical effectiveness of Rhophylac

Erythrocyte clearance

Several studies have shown that Rhophylac rapidly clears Rh D-positive erythrocytes from the circulation (Stucki et al 1998; Miescher et al 2004; CSL Behring UK Ltd 2003). In a study of intravenous or intramuscular Rhophylac 1500 IU in Rh D-negative healthy male volunteers, Rhophylac eliminated Rh D-positive erythrocytes from the circulation a short time after administration (Miescher et al 2004). Ninety-five percent of Rh D-positive erythrocytes were cleared within 8 hours with intravenous administration of Rhophylac, compared with 95% elimination of Rh D positive erythrocytes after 96 hours with intramuscular administration. In another study, in Rh D-negative healthy male volunteers given Rhophylac 1500 IU, more than 99% of Rh D-positive erythrocytes were eliminated within 24 hours of Rhophylac administration, in all but one subject (CSL

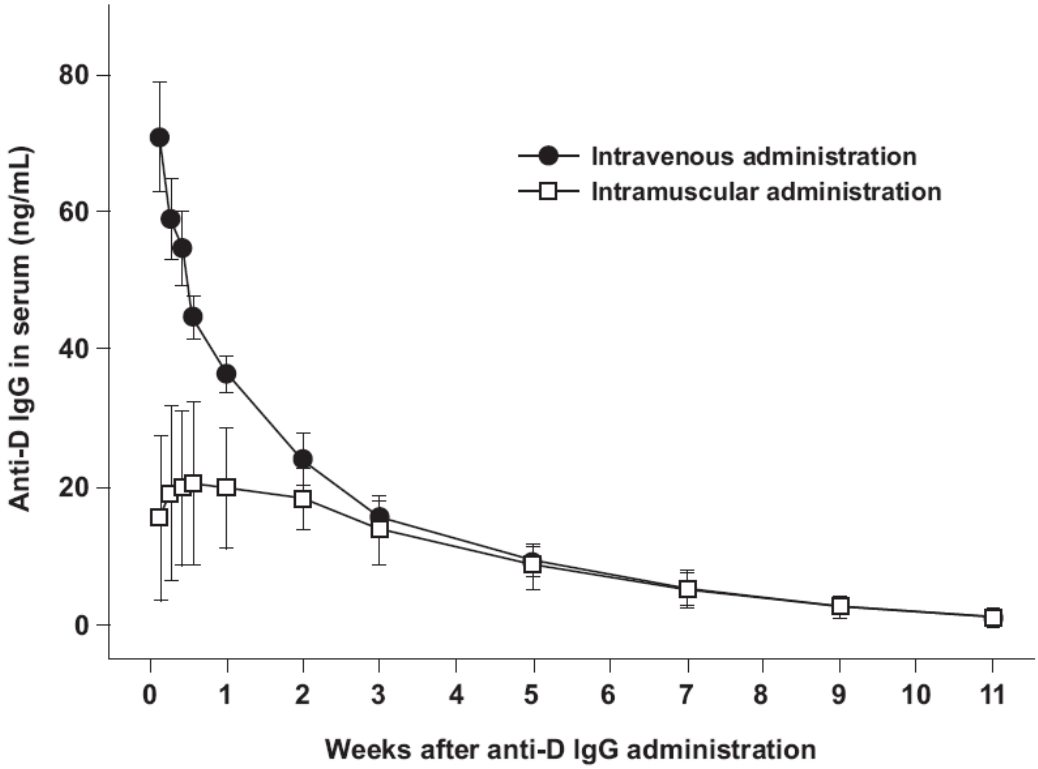
Behring UK Ltd 2003). In a study of Rh D-negative healthy male volunteers, both intravenous and intramuscular administration of Rhophylac 1000 IU at 48 hours after injection of 5 ml of Rh D-positive erythrocytes resulted in rapid clearance of Rh D-positive erythrocytes (Stucki et al 1998). On average, 70% of injected erythrocytes were cleared 2 hours after intravenous administration of Rhophylac. A similar degree of erythrocyte clearance was measured 12 hours after intramuscular administration of Rhophylac.

These data demonstrate that intravenous and intramuscular Rhophylac rapidly clears Rh D-positive erythrocytes from the circulation.

Clinical effectiveness in RAADP

One study has shown that Rhophylac 1500 IU, when used as a one-dose regimen at 28 weeks' gestation, provides measurable serum anti-D IgG levels up to at least nine weeks after administration (Bichler et al 2003) [Figure 1]. Measurable serum anti-D IgG levels were also reported at, and beyond, 11 weeks post-Rhophylac administration. Another study reported that a one-dose regimen of Rhophylac 1500 IU at 28 weeks' gestation (with a further dose within 72 hours after delivery to a Rh D-positive child) resulted in no cases of Rh D sensitisation (MacKenzie 2004).

Figure 1 Mean (SD) anti-D IgG serum concentrations after intravenous and intramuscular administration of one-dose Rhophylac 1500 IU at 28 weeks' gestation (Bichler et al 2003)



Three studies have shown that one-dose regimens of RAADP 1500 IU at 28 weeks' gestation are effective in reducing Rh D sensitisation rates, which ranged from 0-0.3% with RAADP, compared with 1.7-1.8% with no RAADP (Table 4) (Bowman and Pollock 1978; Bowman and Pollock 1987; Trolle 1989). In addition, two separate studies of one-dose regimens of RAADP 1500 IU at 28 weeks' gestation reported that 44% and 35.6% of women had detectable anti-D IgG at delivery (Kennedy et al 1998; Witter et al 1990).

These data demonstrate that one-dose RAADP 1500 IU regimens, including Rhophylac, are effective in preventing allo-immunisation during pregnancy.

Table 4. RAADP studies using one-dose regimens

Source	Anti-D prophylaxis group		Control group (No RAADP)	
	N	% Sensitised	N	% Sensitised
Bowman et al (Bowman and Pollock 1978)	1804	0.3	3533	1.8
Bowman and Pollack (Bowman and Pollock 1987)	9303	0.3	3533	1.8
Trolle (Trolle 1989)	346	0.0	354	1.7

One-dose versus two-dose RAADP regimens

There are no published studies comparing one-dose and two-dose RAADP regimens. However, a meta-analysis has been performed by The Trent Institute for Health Services Research, which included data from 11 relevant identified studies (Chilcott et al 2003). The studies were divided into three groups:

- Group 1: consisting of 6,400 women, which included results from four studies (one randomised and three non-randomised) using anti-D IgG 500 IU at 28 and 34 weeks
- Group 2: consisting of 11,400 women, which included results from three non-randomised studies using a single dose of anti-D IgG 1500 IU at 28 weeks
- Group 3: consisting of 4,700 women, including the results from two community-based studies using anti-D IgG 500 IU at 28 and 34 weeks' gestation

Results from the meta-analysis showed that RAADP significantly reduced the rate of Rh D sensitisation, compared with no routine RAADP (Figure 2). In addition, sensitisation rates were low with no significant difference between anti-D 1500 IU IgG at 28 weeks'

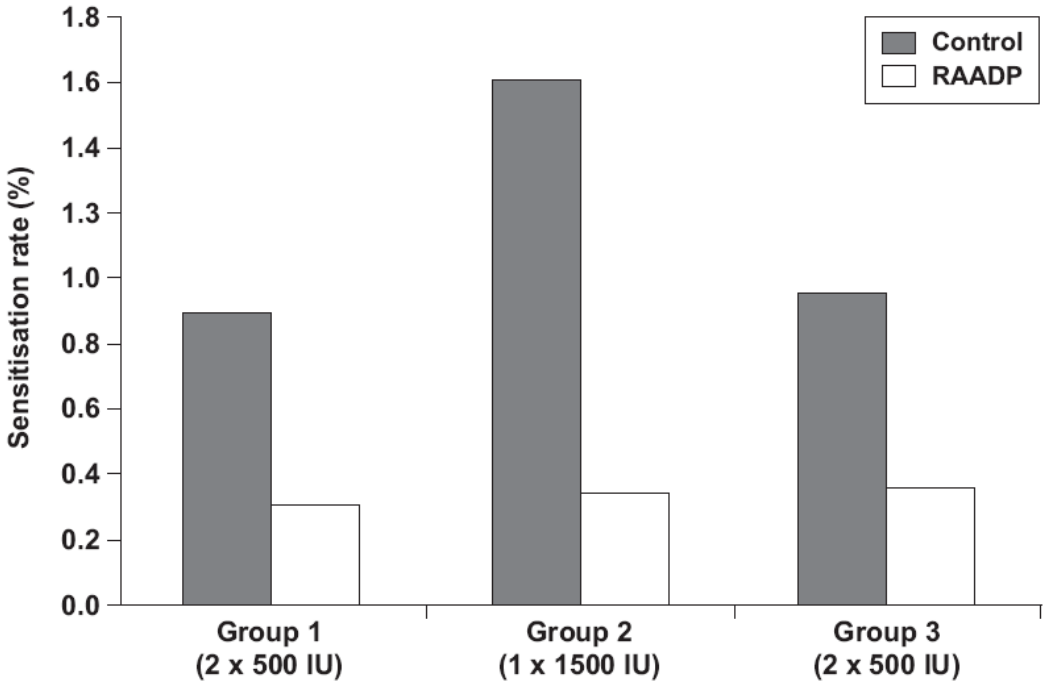
gestation (0.34%), compared with 500 IU anti-D IgG at 28 and 34 weeks' gestation (0.30% and 0.35%) (Table 5).

Table 5. Odds ratio of sensitisation with RAADP from the meta-analysis by Chilcott et al. (Chilcott et al 2003)

	Group 1	**Group 2**	**Group 3**
	Anti-D IgG 500 IU at 28 and 34 weeks'	**Anti-D 1500 IU IgG at 28 weeks'**	**Anti-D IgG 500 IU at 28 and 34 weeks'**
Sensitisation rate of RAADP group (meta-analysis data)	0.30%	0.34%	0.35%
OR of sensitisation with RAADP (95% CI)	0.33 (0.20, 0.55)	0.20 (0.13, 0.29)	0.37 (0.21, 0.65)

OR, odds ratio, CI, confidence interval

Figure 2. Meta-analysis results of Rh D sensitisation rates in three treatment groups (Chilcott et al 2003)



Clinical pharmacokinetic properties of Rhophylac

Clinical pharmacokinetic studies of Rhophylac have shown that a single antenatal dose of 1500 IU administered at Week 28 of gestation results in quantifiable serum levels of anti-D IgG during the last trimester of pregnancy (Bichler et al 2003). This one-dose regimen resulted in quantifiable anti-D IgG serum concentrations up to at least nine weeks after Rhophylac administration, with anti-D IgG concentrations ranging from 0.58 to 4.92 ng/mL (Bichler et al 2003). Quantifiable anti-D IgG levels were also reported at, and beyond, 11 weeks post-Rhophylac administration. At 11 weeks, quantifiable anti-D IgG serum concentrations were found in 6/10 women with trace concentrations (<0.4 ng/ml) in a further 3/10 women. The mean period with anti-D IgG concentrations above 1 ng/mL was 66.5 days (9.5 weeks) and 65.3 days (9.3 weeks), respectively, for intramuscular and intravenous Rhophylac. Pharmacokinetic data after intramuscular and intravenous administration of Rhophylac are shown in Table 6).

Table 6. Pharmacokinetic properties of Rhophylac

Parameter	Intramuscular injection (mean ± SD)	Intravenous injection (mean ± SD)
C_{max} (ng/mL)	70.9 ± 8.2	22.1 ± 12.0
T_{max} (days)	1.0*	5.5*
$T_{1/2}$ (days)	16.4 ± 4.0	17.6 ± 5.0
AUC (day*ng/mL)	1014 ± 146	689 ± 251

*Median value

C_{max}, maximal serum concentration of anti-D IgG; t_{max}, time to maximal serum concentration; $t_{1/2}$, Terminal elimination half-life; AUC, area under the anti-D IgG serum concentration-time curve

Compliance and two-dose regimens

Compliance is an important consideration for RAADP, particularly with regards to the logistics of administering the correct dose at the correct time. Both the one- and two-dose regimens provide equivalent protection for a period of at least 12 weeks, but anti-D IgG needs to be administered at the correct gestational age (MacKenzie 2004). If the timing is wrong, the patient is at increased risk of Rh D sensitisation.

Two studies have shown that compliance rates are relatively low with the two-dose regimen (MacKenzie et al 2006; MacKenzie et al 1999). The first community-based study during 1992-1996, evaluating compliance with a two-dose regimen of anti-D IgG 500 IU at 28 and 34 weeks, reported that approximately one-third of women received both injections at the correct gestational time (Table 7) (MacKenzie et al 1999).

An extension of the same study during 1997-2003, demonstrated that with increasing experience and education, a significant improvement in the timing of the first, and second injections occurred (MacKenzie et al 2006). However, there remained approximately 10% of cases where there was no documented evidence that the 28-week gestation injection had been given and 13-19% of cases with no documented evidence that the 34-week gestation injection had been given. To date, there have been no studies comparing

compliance between one-dose and two-dose regimens. However, implementation of a one-dose regimen may be simpler and less prone to error than the two-dose regimen (MacKenzie 2004).

Table 7. Compliance with a two-dose regimen of anti-D IgG in a community-based study (MacKenzie et al 1999)

Injections of anti-D IgG	Percentage of women
First injection received	89%
Both injections received	76%
Both injections at the correct time	29%

National guidelines in the UK

Current national guidelines in the UK

Current NICE guidelines recommend antenatal prophylaxis at 28 and 34 weeks of gestation (National Institute for Clinical Excellence 2002). The document acknowledges that two doses of anti-D immunoglobulin 500 IU at 28 and 34 weeks into pregnancy appear to be as effective as one 1500 IU dose at 28 weeks. Recent guidelines by the British Committee for Standardisation in Haematology (BCSH) recommend that a single dose of 1500 IU anti-D IgG, given intramuscularly at 28 weeks, may be an effective alternative RAADP regimen that potentially offers cost and logistic benefits.

Rhophylac is currently used by 71 centres throughout England and Wales (see Appendix B).

Case example 1. A clinical consensus has been reached in a Welsh NHS Trust to implement 1500 IU doses of antenatal anti-D prophylaxis following an option appraisal of anti- D products on the market (Brunsdon 2007). The Trust carried out an appraisal of different RAADP regimens (two-dose 500 IU, two-dose 1250 IU, one-dose Rhophylac 1500 IU, or do nothing) using a scoring method that categorised the benefits of RAADP

by significance and then allocated a weighting to each benefit. Each regimen was then allocated a separate score according to the compliance to each benefit and the regimens given a ranking. The one-dose Rhophylac 1500 IU regimen was ranked as the preferred option on the basis of the perceived benefits, including compliance with NICE guidelines, reduced incidence of haemolytic disease of the newborn, optimal use of midwifery time, optimal use of financial resources, ability to overcome poor compliance/uptake, and improved record keeping/audit trail (Table 8).

Case example 2. Another NHS Trust in Wales has successfully implemented a one-dose RAADP 1500 IU regimen with Rhophylac. This particular regimen was chosen because it was perceived that compliance would be better with the one-dose regimen compared with two-dose regimens, the syringes were pre-filled (therefore less time was involved and administration was easier), and it was considered to be cost-effective. To ensure that such a regimen is implemented successfully elsewhere, the Trust recommend that one person should lead the RAADP programme, and that the regimen of choice should have good compliance, be easy and simple to use. Finally, follow-up audits should be carried out to assess performance. The initiative is described here: http://www.blood.co.uk/hospitals/library/pdf/training_education/Kindry_Dennett.pdf

Table 8. Benefit scoring matrix results from a Welsh NHS Trust (Brunsdon 2007)

Regimen	Compliance with NICE guidelines	Reduced incidence of haemolytic disease of the newborn	Optimal use of midwifery time	Optimal use of financial resources	Overcome poor compliance/ uptake	Improve record keeping/ audit trail	Total score	Rank
Two-dose 500 IU	200	210	60	30	160	70	730	**3**
Two-dose 1250 IU	200	270	60	30	160	90	810	**2**
Single-dose 1500 IU	180	240	120	40	180	80	840	**1**
No intervention	20	30	150	50	20	10	280	**4**

National guidelines outside the UK

Practice guidelines and one-dose RAADP practice outside the UK

One-dose 1500 IU RAADP regimens are recommended in guidelines for RAADP in the United States, Canada, France, Switzerland and Germany, demonstrating that one-dose RAADP 1500 IU is widely accepted (Table 9).

Table 9. Practice guidelines recommending one-dose regimens for RAADP outside the UK

Country	Society	Specific guideline	Strength of recommendation
United States	American College of Obstetricians and Gynaecologists (ACOG 1999)	Rh D-negative women who are not Rh D-alloimmunised should receive anti-D IgG 1500 IU at approximately 28 weeks of gestation, unless the father of the baby is also known to be Rh D-negative	A
United States	American Society of Clinical Pathologists (Hartwell 1998)	Antepartum administration of a standard 1500 IU dose (intravenous or intramuscular) anti-D IgG is indicated between 28 and 30 weeks of gestation in all pregnant Rh D-negative women who have not already developed anti-D	Not reported
Canada	Society of Obstetricians and Gynaecologists of Canada (SOGC 2003)	Anti-D IgG 1500 IU (intravenous or intramuscular) should be given routinely to all Rh D-negative nonsensitised women at 28 weeks gestation when foetal blood type is unknown or known to be Rh D-positive	IA

France	Collège National des Gynécologues et Obstétriciens Français (CNGOF 2005)	Any Rh D-negative pregnant woman, not immunised against antigen D and whose foetus is known or suspected to be Rh D-positive, will be offered an intramuscular anti-D immunoglobulin injection of 1500 IU at 28 weeks' gestation (+/- 1 week)	A
Switzerland	Akademie Feto-Maternale Medizin (Akademie Feto-Maternale Medizin 2005)	Anti-D should be administered between 28 and 30 weeks of gestation	Not reported
Germany	Des Bundesausschusses der Ärzte und Krankenkassen (des Bundesausschusses der Ärzte und Krankenkassen 2003)	If in an Rh D-negative pregnant woman, no anti-D antibodies are detectable, then in Week 28 to 30 of pregnancy, a standard dose (about 300 µg) of anti-D immunoglobulin should be injected to prevent a sensitization before birth	Not reported

Level A evidence: recommendation is based on good and consistent evidence; Level of evidence I: evidence obtained from at least one properly randomised, controlled trial; Not reported: the strength of the evidence in the recommendation was not provided.

Cost-effectiveness of RAADP

It is well established that RAADP is a cost-effective intervention for haemolytic disease of the newborn in pregnant women who are Rh D-negative (Chilcott et al 2004). There is limited comparative evidence of the cost-effectiveness of one-dose and two-dose RAADP regimens.

Two studies have reported that one-dose RAADP regimens are more cost-effective than two-dose regimens (Brunsdon 2007; Vick et al 1996). One cost-effectiveness study has evaluated the cost-effectiveness of three different RAADP regimens (two-dose RAADP 500 IU at 28 and 34 weeks' gestation, two-dose RAADP 1250 IU at 28 and 34 weeks' and one-dose RAADP 1250 IU at 28 weeks' gestation). In this study, the one-dose RAADP 1250 IU was more cost-effectives than the two-dose RAADP 500 IU regimen, which was in turn more cost-effective than the two-dose RAADP 1250 IU regimen (Table 10) (Vick et al 1996).

Table 10. Cost-effectiveness of one-dose and two-dose RAADP regimens (Vick et al 1996)

RAADP regimen	Incremental cost per Rh D-sensitisation prevented
One-dose RAADP 1250 IU	£1188
Two-dose RAADP 500 IU regimen	£2781
Two-dose RAADP 1250 IU	£5414

The second study used a benefit scoring matrix and estimated total costs and optimal use of financial resources with one-dose RAADP 1500 IU (Rhophylac), compared with the two-dose 500 IU regimen and two-dose 1250 IU regimen (Brunsdon 2007) (Table 11).

Table 11. Estimated total costs and use of financial resources with one-dose and two-dose RAADP regimens (Brunsdon 2007;manuscript in preparation)

	One-dose RAADP 1500 IU	Two-dose 500 IU regimen	Two-dose 1250 IU regimen
Optimal use of financial resources score	40	30	30
Total costs	£43,866.3940	£57,341.35	£57.341.35

Impact on the National Health Service

If RAADP is given to all pregnant women who are Rh D negative, the total gross cost of drugs, using the NHS list price is estimated to be approximately £5.7 million for the 2 x 500 IU regimen and £5.1 million for the 2 x 1250 IU regimen using 2002 estimates of costs (Chilcott et al 2003). The total administration cost, based on an estimate of £10 per pregnant woman treated would be £1.1 million. Cost savings of £400,000 have been estimated from reductions in haemolytic disease of the newborn. Thus, the total net cost to the NHS in England and Wales would be £5.6 to 6.4 million per year (Chilcott et al 2003). Recent guidelines by the BCSH highlight that a single dose of 1500 IU anti-D, given intramuscularly at 28 weeks, potentially offers cost and logistic benefits (BCSH 2006).

Conclusions

- RAADP is effective in preventing haemolytic disease of the newborn
- Clinical efficacy data shows no significant difference in sensitisation rates between one-dose and two-dose regimens
- One-dose Rhophylac 1500 IU is clinically effective, safe, easy to administer, and cost-effective
- One-dose regimens are widely implemented in clinical guidelines outside of the UK
- Compliance with the two-dose regimen appears to be low and the one-dose regimen may be more cost-effective

Implementation of a one-dose RAADP regimen is safe and effective, may be simpler, may lead to fewer administration errors, and may be more cost-effective than two-dose RAADP regimens. We respectfully request that Rhophylac be considered for inclusion in the updated guidelines.

Appendices

Appendix A. Publications and clinical study data

Study ID	Data source	Comments
Study ZLBB 621	Stucki et al. 1998 (Stucki et al 1998)	Clinical study of Rhophylac in male volunteers
Study ZLB 00_032	CSL Behring 2003 (CSL Behring UK Ltd 2003)	Clinical study of Rhophylac in male volunteers
Study ZLB 622	CSL Behring 1996 (CSL Behring UK Ltd 1996)	Clinical study of the post-partum efficacy of Rhophylac
Study ZLB 98_011	MacKenzie et al 2004 (MacKenzie et al 2004)	Clinical study of antenatal and postnatal efficacy
Study ZLB 98_012	Bichler et al 2003 (Bichler et al 2003)	Determination of serum concentrations of anti-D after ante-partum administration of Rhophylac
Study ZLB 039	Miescher et al 2004 (Miescher et al 2004)	Erythrocyte clearance study in male volunteers
NA	Bowman et al (Bowman and Pollock 1978)	One-dose RAADP 1500 IU study in Rh D-negative pregnant women
NA	Bowman and Pollock (Bowman and Pollock 1987)	One-dose RAADP 1500 IU study in Rh D-negative pregnant women
NA	Trolle et al (Trolle 1989)	One-dose RAADP 1500 IU study in Rh D-negative pregnant women
NA	Chilcott et al (Chilcott et al 2003)	Systematic review of RAADP in Rh D-negative pregnant women

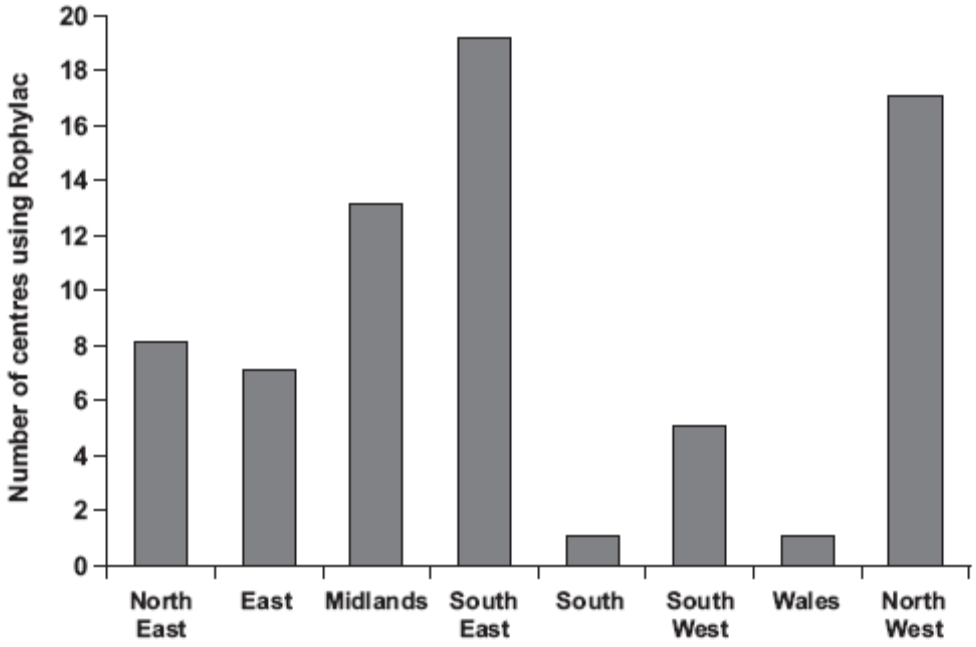
NA	Kennedy et al (Kennedy et al 1998)	Clinical study of one-dose regimens of RAADP 1500 IU at 28 weeks' gestation
NA	Witter et al (Witter et al 1990)	Clinical study of one-dose regimens of RAADP 1500 IU at 28 weeks' gestation
NA	Bowman et al (Bowman and Pollock 1978)	Clinical study of one-dose regimens of RAADP 1500 IU at 28 weeks' gestation
NA	Bowman and Pollack (Bowman and Pollock 1987)	Clinical study of one-dose regimens of RAADP 1500 IU at 28 weeks' gestation
NA	Trolle (Trolle 1989)	Clinical study of one-dose regimens of RAADP 1500 IU at 28 weeks' gestation
NA	American College of Obstetricians and Gynaecologists (ACOG 1999)	Guidelines on RAADP in the United States
NA	Hartwell et al (Hartwell 1998)	Guidelines on RAADP in the United States
NA	Society of Obstetricians and Gynaecologists of Canada (SOGC 2003)	Guidelines on RAADP in Canada
NA	Collège National des Gynécologues et Obstétriciens Français (CNGOF 2005)	Guidelines on RAADP in France
NA	Akademie Feto-Maternale Medizin (Akademie Feto-Maternale Medizin 2005)	Guidelines on RAADP in Switzerland

N/A	Des Bundesausschusses der Ärzte und Krankenkassen (des Bundesausschusses der Ärzte und Krankenkassen 2003)	Guidelines on RAADP in Germany
NA	Vick et al (Vick et al 1996)	Cost-effectiveness study of one-dose vs. two-dose RAADP regimens
NA	Brunsdon K(Brunsdon 2007)	Clinical and cost-effectiveness study of anti-D prophylaxis

NA, not applicable; RAADP, routine antenatal anti-D prophylaxis

Appendix B

Distribution of clinical centres using Rhophylac in England and Wales



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