Submission to NICE

on

The Use of Anti-D as Routine Antenatal Prophylaxis (RANP)

to aid

Updating Technology Appraisal Guidance

Submitted by:

[redacted]

on behalf of

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Background

Bio Products Laboratory (BPL) is a not-for-profit, government-owned plasma fractionation unit which is an operating division of NHSBT (National Health Service Blood and Transplant) a Special Health Authority within the NHS.

Anti-D, for intramuscular administration, has been manufactured by BPL on the Elstree site since its introduction into clinical medicine in the late 1960s. The product was used in accordance with the national guidelines available during this period which included use during pregnancy for potentially sensitising events and postnatal prophylaxis. A Product Licence variation to include routine antenatal prophylaxis, 500 IU at 28 and 34 weeks, as an indication was approved by MHRA on 28th June 1993.

In 1998, BPL stopped using plasma from England & Wales to manufacture plasma-derived products because of the appearance of vCJD in the UK population and uncertainty about whether this condition could be transmitted by plasma products. UK plasma has not been fractionated by BPL since May 1998. In December 1998, but it was reinstated in April 1999, once product manufactured from US plasma became available (a precautionary measure). Since then, only plasma from USA has been used by BPL. In 2001, the Department of Health purchased some plasma collection centres in the USA to ensure a continued supply of plasma for BPL. Now, most of the plasma used by BPL comes from these FDA-licensed and MHRA-audited facilities in the USA

In July 2001, BPL was granted a product licence variation, namely the incorporation of a solvent/detergent step in the process. This variation was purely as a safeguard against the transmission of lipid-enveloped viruses and in line with anticipated regulatory requirements, although there had been no substantiated reports of virus transmission involving BPL's anti-D product over the previous decades. International experience with immunoglobulins for intramuscular administration over decades reveals freedom from virus transmission (unlike, for example, coagulation products).

BPL has four presentations of their anti-D product, now called D-Gam®, licensed by the MHRA. The vial sizes are nominal 250 IU (PL 08801/0047), 500 IU (PL 08801/0048), 1,500 IU and 2,500 IU (PL 08801/0049). The 500 IU vials are licensed by MHRA for routine antenatal administration at 28 and 34 weeks of gestation of non-sensitised Rh negative women. The 1,500 IU and 2,500 IU presentations are currently licensed to provide larger postnatal doses conveniently when a large fetomaternal haemorrhage (FMH) has been found. The 500 IU dose is also licensed for routine postnatal administration to Rh negative women who have just delivered a Rh positive baby and for prevention of sensitisation during the second half of pregnancy if any potentially sensitising event or occurs or intervention is needed. Finally, the 250 IU dose is licensed for prophylaxis of potentially sensiting events in the first half of pregnancy (up to 20 weeks). All these indications are also part of the national recommendations from the Royal College of Obstetricians and Gynaecologists (RCOG). Thus, BPL provides a range of doses to optimise use at all stages of pregnancy.

BPL is now the only fractionator of anti-D in the UK since the closure of the Scottish facility, the Plasma Fractionation Centre (PFC), in January 2006, which was part of the Scottish National Blood Transfusion Service (SNBTS).

Anti-D is also licensed in the UK from some internationally based organisations.

After the last 'Guidance on the use of routine antenatal anti-D prophylaxis for RhD-negative women' (Technology Appraisal Guidance No 41) from NICE in May 2002, BPL has noticed a gradual increase in the uptake of their 500 IU D-Gam product. During the 12 months from October 2003 to September 2004 the issues of 500 IU vials was more than twice those for the 12 months from October 1999 to September 2000. This reflects the increasing number of UK hospitals introducing a programme of routine antenatal prophylaxis (500 IU at weeks 28 and 34 gestation), in keeping with the guidelines.

New information

Diagnostic test for fetal Rh status

At the moment it is not practical to identify the Rh status of the fetus in Rh negative women. However, the new diagnostic technology, mentioned in BPL's Comment Form in April 2007 (see Appendix 2), would have a significant impact on the use of anti-D. This technology is aimed at identifying the Rh status of the fetus from a sample of maternal blood. Not only would the routine antenatal use of anti-D be reduced, but also the use for potentially sensitising events. Depending on the period of gestation at which the diagnostic test would be able to reliably detect the appropriate fetal DNA in maternal blood would determine what impact there would be on the use of anti-D in early pregnancy.

Before the introduction of the test it will be essential to have the test able to be performed in routine laboratories which handle maternal specimens. It is also very important to be sure that the test has appropriate sensitivity and specificity when performed in such laboratories because the risk of sensitisation would return if anti-D is not then used at that time. It will still be very important to use anti-D in compliance with the current guidelines if (a) no test is done, (b) an equivocal result is obtained or (c) the fetus is confirmed as Rh positive. Finally, the cost of the procedure will need to be carefully assessed in relation to all the other procedures it would replace.

Safety information of BPL's D-Gam®

The last official safety update for D-Gam which was prepared according to the international regulations for medicinal products covered the period from 1 October 1999 to 31 March 2005. During these 66 months, BPL received 15 reports of adverse events related to Anti-D Immunoglobulin, five of which were classed as 'serious' according to the ICH definition. Nine cases involved pruritic dermatological reactions (urticaria – 5 cases; pruritic rash – 2 cases and pruritus – 2 cases). There was no discernible pattern to the other reports: one case of a probable anaphylaxis, one report of a possible

anaphylactoid reaction and one case with tongue swelling. There were no reports of potential virus transmission.

All of BPL's anti-D issued over this period (>700,000 vials) was manufactured from plasma collected in the USA. It has been estimated that more than 350,000 subjects received BPL's product during this period.

None of the product-related adverse events reported were not already included on the Summary of Product Characteristics (SPC). So there were no 'new' reactions.

BPL has carried out a risk assessment of the probability of HCV infection in its products, including D-Gam®. The risk is infinitesimally small. The report can be supplied on request, in confidence.

Therefore, based on BPL's experience, the risks from anti-D are small, when it is administered in accordance with national guidelines and the prior NICE appraisal recommendation.

The Department of Health commissioned DNV to prepare a risk assessment of vCJD in blood and plasma-products which was published in February 2003. It is available on the following website: www.dnv.com and can be found in the section on 'Risk of infection from variant CJD in blood'.

Current NHS price of D-Gam
The current price for 500IU D-Gam is £19.50 /vial.

Current uptake of RANP
Information available to BPL indicates that of the hospitals that have implemented RANP, 55% are using D-Gam 500 IU at 28 and 34 weeks gestation.

The dose of anti-D to be administered
Particularly since the implementation of anti-D for routine antenatal prophylaxis, there have been a number of requests for clarification of the dose which the midwife should administer.

As mentioned above, the dose is always referred to as 500 IU, for example. Practice over the decades has been to administer the contents of the vial as THE dose. It has been assumed that the dose in the vial is precisely 500 IU. However, because anti-D is a biological product and not a pharmaceutical the tolerances on the amount in the vials are wider. The actual dose in a vial from different batches will not be the same, but it will always be within the licensed specification. Simply this means that at the end of the shelf-life of the product, there will be at least 500 IU available to be drawn up into a syringe. Nowadays, the actual potency of the batch has to be printed on the vial with the actual volume that will deliver the nominal 500 IU dose. The confusion arises because midwives are trained to give the precise dose, *i.e.* 500 IU as stated in the 'guidelines' or Trust 'policy'. They sometimes struggle to understand that administering the contents of

the whole vial is what has been happening since the late 1960s. Any support for simplification that the NICE appraisal might be able to provide would be welcome.

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