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Dear Mr Feinmann

This letter sets out Baxter Healthcare's response to the NICE review of guidance for routine antenatal anti-D prophylaxis (RAADP) for rhesus-negative women (TA41, issued May 2002).

In line with guidance for manufacturers, 'commercial in confidence' information is underlined. 'Commercial in confidence' information is also italicised to distinguish it from underlined headings.

Executive summary

- Baxter Healthcare supports the existing recommendations for RAADP for rhesus-negative women, and believe that the current review should continue to recommend routine prophylaxis in this population
- The current review of cost-effectiveness should include careful consideration of the following:
    - The actual cost to the NHS of anti-D immunoglobulins reflects the pricing achieved through competitive tender between suppliers
    - The total cost of preventing sensitisation in RhD-negative women should reflect the use of one dose of anti-D post-partum in addition to either the one- or two-dose antenatal regimen
    - Across the total patient population, even allowing for any potential reduced compliance or mis-timing of delivery of anti-D immunoglobulin, RAADP remains highly cost effective

- Given there are only three suppliers of anti-D immunoglobulin to the NHS, and with minimal cost-effectiveness differential between them, it is vital that NICE make no preferential recommendation of one product over another which might discourage any supplier from maintaining their supply to the NHS. The current plurality within the market place serves to maintain ongoing supply of anti-D, allowing Trusts to negotiate market competitive prices of anti-D immunoglobulin for their patients

Background

RhD-negative women who are pregnant with an RhD-positive foetus may become sensitised following the passage of foetal red blood cells into the maternal circulation. In subsequent pregnancies, maternal antibodies may cross the placenta and, if the foetus is RhD-positive, cause haemolytic disease. Approximately 17% of women giving birth in England and Wales are RhD negative. Of these, 59% will have RhD-positive babies and are, therefore, at risk of sensitisation: this represents about 10% of all births each year in England and Wales. Consequences include haemolytic disease of the foetus and neonate, pregnancy loss, and premature birth and its associated complications. Anti-D immunoglobulin prevents development of maternal antibodies by 'mopping up' any RhD-positive foetal cells in the maternal circulation.

Previous NICE guidance

Guidance TA41 recommended that RAADP is offered to all non-sensitised, RhD-negative pregnant women. RAADP is currently a dose of anti-D immunoglobulin of at least 500 international units (IU) at 28- and 34-weeks gestation. An alternative schedule is a single dose of at least 1500 IU at weeks 28–30.

The current appraisal scope includes two anti-D immunoglobulin products marketed and distributed by Baxter in the UK – Partobulin SDF (manufactured by Baxter AG, Vienna), and WinRho SDF (manufactured by Cangene Corp, Winnipeg). These two products have different presentations and licensed uses, and are marketed for two separate indications.

Baxter is submitting this letter to NICE rather than full detailed submissions for the reasons outlined below.

A submission was made to NICE for the product now known as Partobulin SDF as part of TA41. The document is attached as an appendix to this letter and should be referenced in the current review, as the majority of the information remains valid and unchanged.

Product modification

Whilst no new clinical data have become available since guidance was issued in May 2002, there has since been a change to the product licence in light of a modification to the product to include the following additional manufacturing steps:

- Solvent/detergent treatment
  Ensures the inactivation of lipid-enveloped viruses, such as Hepatitis B, Hepatitis C and HIV.

- Nanofiltration
  Validated to minimise the risk from non-enveloped viruses, such as Hepatitis A and Parvovirus B19 (which is associated with additional pregnancy complications).

The modified preparation, Partobulin SDF, brings the product in line with other European countries with respect to enhanced viral screening, and was granted a type 2 licence variation in February 2004. Baxter would like to stress that the pharmacokinetic profile of the product remains the same, and that a study to investigate the pharmacokinetic profile of the new solvent/detergent (S/D) formulation concluded that results are comparable with published data of the non-S/D-treated predecessor product.[1] There is also no change to the product's safety profile.

List price change and effect on economic analyses

Prior to Partobulin SDF modification, Baxter Anti-D was marketed in the UK as a standard 1250 IU dose presented in a pre-filled syringe for ease of use. The NHS pack cost was £23.90. Following the modification, the list price was increased to £35.00. Baxter appreciates that the increase in list price affects the cost-effectiveness analysis and budget impact analysis for Partobulin SDF. Using the original model that was submitted for TA41, the cost per QALY of RAADP for all RhD-negative women is £5,742, reducing to £3,181 for primigravidae only. The total cost of implementing RAADP in England and Wales is around £7.8 million for all RhD-negative women, reducing to £3.3 million for primigravidae only.

It was decided to use the original model after checking that key assumptions were still valid and had not changed beyond the degree where they would affect the overall conclusion of the results.

[1] Jilma-Stohlawetz P et al. Pharmacokinetics (PK) of S/D treated anti-D immunoglobulin after intramuscular injection in healthy volunteers: gender differences in PK. Transfus Apher Sci 2005;33(2):135–40.

Baxter would also like to emphasise that despite the list price being used for the economic analysis, actual prices, and therefore actual cost to the NHS, are subject to contract negotiations.

[redacted]

[redacted]

Total treatment cost versus RAADP cost

As a post-partum dose of anti-D is also required to complete the treatment of RhD-negative women, the additional cost of this dose should also be taken into account when comparing costs of the different dose regimens. Rather than a one- versus two-dose comparison, the true cost comparison should be two doses versus three, making the cost differential between the different dosing regimens much smaller than otherwise might appear.

[redacted] Using the list price the cost comparison would be £105 (Partobulin SDF) compared with £93 (Rhophylac).

In light of this, Baxter believes that use of Partobulin SDF as routine antenatal anti-D prophylaxis is still highly cost-effective when compared with other therapies and disease areas.

Baxter also notes comments on the appraisal scope relating to differing dose regimens (once vs. twice administration) and possible implications on compliance.

One dose versus two doses

The benefits of single dosing at 28–30 weeks versus doses administered at 28 and 34 weeks gestation remain unproven. A meta-analysis looking at the efficacy of routine antenatal prophylaxis concluded there was no difference in efficacy

between the one- or two-dose regimens.[2] This is supported by the British Committee for Standards in Haematology (BCSH), who acknowledge that the single dose administration *may* be an effective alternative, but that more evidence is required to establish its comparative efficacy.[3]

Compliance

On the issue of compliance benefits through single dose administration, it should be noted that administration of anti-D therapy usually takes place at scheduled antenatal visits and, as such, does not place an added resource burden on the NHS. Additionally, the potential impact of non-compliance does not adversely impact the cost-effectiveness of RAADP.

Two community-based studies showed that missed and mis-timed doses lead to higher sensitisation rates.[4,5] The potential implications of this are two-fold: the cost of implementing RAADP will be less than the cost presented in a budget impact analysis due to less doses being administered; and the likelihood of increased sensitisations will adversely affect the cost-effectiveness argument i.e. increase the cost per QALY.

However, both these studies examining compliance achieved sensitisation rates of around 0.4% during periods of reduced compliance and mis-timing, compared with the 0.24% used in the baseline calculation of cost-effectiveness. The cost per QALY under this scenario lies between £3,886 (primigravidae only) and £6,453 (all RhD-negative women) using published list price.

It can be concluded therefore that implementation of RAADP will remain highly cost-effective for all scenarios even if reduced compliance and mis-timing of dose causes higher than optimal sensitisation rates.

Supply issues

Notwithstanding clinical evidence in terms of efficacy, cost, and compliance, a critical issue for consideration is the maintenance of supply of immunoglobulin. Therefore any recommendation which favoured one anti-D over another could

[2] Chilcott J et al. A review of the clinical effectiveness and cost-effectiveness of routine anti-D prophylaxis for pregnant women who are rhesus-negative. Health Technol Assess 2003;7(4):iii–62.
[3] British Committee for Standards in Haematology Guidelines for the use of prophylactic anti-D immunoglobulin, 2006.
[4] MacKenzie IZ et al. Routine antenatal Rhesus D immunoglobulin prophylaxis: The results of a prospective 10-year study. Br J Obstet Gynaecol 1999;106(5):492–7.
[5] Mayne S et al. Rate of RhD sensitisation before and after implementation of a community based antenatal prophylaxis programme. BMJ 1997; 315(7122):1588.

jeopardise the plurality within the marketplace. In such a situation, not only could the overall availability of anti-D to the UK be threatened, but this could also affect the competitive nature of the pricing in a tender-driven market.

There have been numerous examples of disruptions to supply of immunoglobulins. At the time of writing, the largest supplier of plasma products to the UK Bio Products Laboratory (BPL; supplier of D-GAM), have communicated that it is currently able to meet only 50% of some customers' anti-D requirements[6]. Anti-D supplies were also severely limited during the late 1990s variant CJD scare. Additionally, though not directly relevant to this review, BPL has informed its customers that due to a shortage of anti-tetanus immunoglobulin, it is currently only available for emergency treatment of tetanus infection. This is one example of how disruption of immunoglobulin supply may jeopardise public health.

There are only 3 suppliers of anti-D immunoglobulin to the NHS. With no evidence to suggest the benefit of one over another, and in order to maintain ongoing supply of anti-D at market competitive prices to the UK, Baxter believes that all formulations should be recommended by NICE.

WinRho SDF

WinRho SDF, although licensed for use as RAADP, is the only anti-D immunoglobulin licensed in the UK for the treatment of a clotting disorder called Immune Thrombocytopenic Purpura (ITP). Since WinRho SDF is marketed and used solely for this condition, it is priced specifically for this market.

WinRho SDF is administered intravenously for ITP and is used as an alternative treatment to intravenous human normal immunoglobulin (IVIG) in the treatment of this disorder.

Baxter believes there is no use of WinRho SDF during pregnancy as RAADP for rhesus-negative women in the UK. Despite the inclusion of the product in this review, use of WinRho SDF should not routinely be considered for this indication. However, Baxter believes that if there were disruptions to supply of the other three available products, then WinRho SDF could provide an alternative to supplement anti-D supplies. Such an arrangement already exists in countries such as New Zealand,[7] where production levels of anti-D immunoglobulin are insufficient to ensure continuity of supply.

Baxter would therefore like to see a recognition that WinRho SDF is primarily indicated for the treatment of ITP and should not routinely be used for RAADP; however, in recommendation, WinRho SDF could be used in the event of anti-D immunoglobulin supply problems.

[6] Personal communication with customer.
[7] Supply of Anti-D Immunoglobulin. Blood Issues March 2007, Issue 17.

In summary, Baxter welcomes the ongoing review of the clinical and cost-effectiveness of RAADP – a highly cost-effective treatment in an important disease area. A full submission has not been made, as the majority of information from a previous submission (TA41) remains valid.

Since previous guidance was issued, there have been minimal changes to Baxter's Anti-D. Now named Partobulin SDF, manufacture includes enhanced viral reduction steps and there has been an increase in the list price. Although the economic analysis and budget impact are slightly altered based on the increased list price, this does not significantly change the economic argument. It should also be noted that discounted pricing negotiations reflect required volumes, and as such, the actual cost to the NHS of Partobulin SDF is much lower than that calculated from its list price.

On the issue of dose regimens and compliance, there is still no definitive evidence that one antenatal dose is more effective than two. Furthermore, evidence suggests that reduced compliance does not change the findings that Partobulin SDF given as RAADP is highly cost-effective.

Above all, the most important issue is to ensure ongoing availability of anti-D to the NHS. Given the historic fragility of immunoglobulin supply, Baxter believes that NICE should continue to recommend all formulations of anti-D for RAADP.

With regards to WinRho SDF, Baxter recognises it should not routinely be used for RAADP; however, it may still be a viable alternative where anti-D immunoglobulin supply problems exist.

Baxter Healthcare thanks NICE for the opportunity to present its perspective regarding the review of guidance on RAADP, and welcomes further communication from the review group should additional information or clarification of points arising from this letter be required.

Yours sincerely,

See appendix: "Submission to the National Institute for Clinical Excellence -The clinical and cost effectiveness of Anti-D prophylaxis for Rhesus negative women in pregnancy" (August 2001)