

OCTAPHARMA'S COMMENTS ON THE REPORT ISSUED BY CADTH (CANADA) ON THE COST-EFFECTIVENESS OF OCTAPLAS® COMPARED TO FFP.

Octapharma has read with great interest the report prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH) on the cost-effectiveness of Octaplas® compared to FFP. This is the second version of this cost-effectiveness report, which is entitled "Octaplas Compared with Fresh Frozen Plasma to Reduce the Risk of Transmitting Lipid-Enveloped Viruses: An Economic Analysis and Budget Impact Analysis".

Octapharma extensively reviewed the first version of the report, and a telephone discussion took place in August 2008 between CADTH and Octapharma, during which Octapharma made CADTH aware of some inaccuracies contained in their report.

Octapharma recognizes that CADTH had done some corrections to the first version of the report but, we are at the same time surprised to see that some of the information we provided had not been taken into consideration. We have the following five major concerns with the report:

1. The authors have limited access to the product characteristics of Octaplas® and no clinical experience with the product, and highly experienced European clinicians and national blood banks were not consulted;
2. Peer-reviewed published scientific papers demonstrating a significantly reduced rate of adverse reactions with Octaplas® compared to FFP, were not considered;
3. The report assumes an incidence of TRALI of 1 in 2,850 which in our opinion is too low and fails to recognize the prospective study performed by Gajic which found that 1 in 12 critically ill patients developed TRALI following transfusion with FFP;
4. The report assumes that Octaplas® has the same probability of transmitting HAV and PB19 as FFP; and
5. The report significantly underestimates the cost of Canadian FFP.

The first fact to note is that the assessment has been made by physicians who have limited access to the product characteristics and no clinical experience with its use. Octapharma raised this point with the agency in their draft review period, but we were advised "for budgetary reasons they could not contact European experts". It is, therefore, not surprising that there are fundamental misconceptions lead by the fact that Octaplas® has been in certain ways evaluated under the mistaken assumption that it is identical to the product which was available in the USA: Plas-SD manufactured by Vitex, a product with a different manufacturing process and completely different biochemical characteristics, as confirmed by

experts from the PEI, which experts have also explained the clinical differences observed between both products¹.

In the conclusions contained in the executive summary of the report, one can read that: “the incremental cost per QALY results from low transfusion-related risks for FP (Frozen Plasma) and FFP (Fresh Frozen Plasma) engineered by advances in the safety measures of blood transfusion, such as the testing, donor screening, and deferral”.

However, peer-reviewed published scientific papers demonstrating a significantly reduced rate of adverse reactions with Octaplas[®] compared to FFP were not considered. In page 3, the authors state that they did not find any evidence of a decreased rate of immunological severe adverse reactions and that, after a systematic review of the published literature, they also did not find evidence of any reduction in the rate of adverse events from the use of Octaplas[®].

While not trying to raise suspicions regarding the way that the systematic reviews were performed, we have to state that this is not true – there are a number of peer-reviewed published scientific papers demonstrating a significantly reduced rate of adverse reactions with Octaplas[®] compared to FFP.

Just doing a Google search with the terms: “reduced AND rate AND reactions AND octaplas” leads to the following published peer-reviewed articles:

Cryosupernatant and solvent detergent fresh-frozen plasma (Octaplas) usage at a single centre in acute thrombotic thrombocytopenic purpura.
M. Scully, I. Longair , M. Flynn, J. Berryman & S. J. Machin
Vox Sanguinis 2007; 32:154-158

Fresh-frozen plasma, pathogen-reduced single-donor plasma or bio-pharmaceutical plasma? P. Hellstern
Transfusion and Apheresis Science 2008; 39:69-74

Indications for use and cost-effectiveness of pathogen-reduced ABO-universal plasma
Solheim, Bjarte G; Chetty, Rangini; Flesland, Oystein
Current Opinion in Hematology 2008; 15 612-617

In the above three articles, a reduction in the rate of adverse events arising from Octaplas[®] usage is shown.

Moreover, the hemovigilance data from France² states the advantage of Octaplas[®] over FFP when comparing adverse events. Also during the ISBT Macau congress in June 2008, the Finnish Red Cross presented their data on the reduction of the adverse events after switching the country 100% to Octaplas[®] usage³.

CADTH may say in their defence, that these publications and the hemovigilance data were not published when preparing their report. This may be true for the first release of the report, but not for this final version issued in late 2008 and reviewed

by Octapharma in the beginning of 2009. In addition, Octapharma had warned CADTH of the existence of these data and publications during the telephone conference held when the agency was preparing their second version of the report.

It is also incomprehensible that the authors did not contact the hemovigilance departments of Norway, Finland and other countries with a high proportion of Octaplas® usage to gauge their opinion and capture data regarding the clinical use of Octaplas®.

If the reduction in severe adverse events would have been incorporated into CADTH's economical model, there is no doubt that the numbers would have been very different from what CADTH has reported, making Octaplas® not only more effective than FFP but also less costly.

In the report CADTH uses a probability of TRALI of 0.00035. This corresponds to an incidence of approximately 1:2,850. The fact is that CADTH does not take into consideration the only published clinical paper which uses the TRALI definitions from the Toronto Consensus Conference on TRALI⁴ to estimate the incidence of TRALI among critically ill patients receiving FFP. In this prospective, nested case-control study⁵, Gajic found that 8% of transfused patients developed TRALI after transfusion. This figure may reflect a better approach to the real TRALI incidence in critically ill patients, and is a long way from the 1:2,850 figure used by CADTH. It is widely known and also acknowledged by the FDA that TRALI is still under diagnosed due to a lack of awareness. Octapharma also made CADTH aware of the existence of the Gajic clinical paper during the telephone conference to discuss the report before the final version was issued.

Further, the report estimates that Octaplas® has the same probability of transmitting HAV and PVB19 as FFP. Octapharma has repeatedly communicated to CADTH that there has been no case of infection with either HAV or PVB19 after transfusing more than 6,000,000 units of Octaplas®. As explained to CADTH, in the case of HAV and PVB19, Octaplas® has to be NAT tested for both viruses and the pool needs to have a minimum amount of antibodies against both viruses to assure the immune neutralization of both. Limits for both the NAT testing and the antibodies content are part of the Final Product Specifications of the product. It is worth pointing out that in the PVB19 infections detected after the infusion of solvent-detergent plasma, the product implicated was Plas-SD and that NAT testing was not yet in place for this product at that time. The immune-neutralization of HAV and PVB19 has been recognized as a sufficient measure not only by Health Canada but also many other European Regulatory Agencies to reduce the risk of viral transmission of HAV and PVB19 in pooled plasma.

Finally, from the perspective of cost-effectiveness, we also would like to point out that the assumption used in the CADTH report of \$96 per bag for FFP is inaccurate, as it does not precisely reflect the costs borne by the Canadian healthcare system to produce and distribute a bag of FFP for transfusion into a patient.

From Appendix 2 of the report, it has been assumed by CADTH that the total cost per bag of each type of plasma are as follows:

- Apheresis FFP = \$267;
- Whole blood derived FFP = \$92.

We have some major concerns with the modelling performed by CADTH in this area. Firstly, this figure of \$92 grossly underestimates the costs borne by the Canadian healthcare system to produce and distribute a bag of whole blood derived FFP.

This figure of \$92 consists almost exclusively of overhead of \$84 (Source: Appendix 2, CADTH report). The direct costs are also minimal at \$8, and there is zero cost allocated for testing. Therefore, in the case of recovered FFP, it is clear that:

1. The testing costs of \$67 per unit have been allocated solely to either platelets or the red blood cells, and no part of these costs have been allocated to plasma;
2. The direct costs are extremely low at \$8, especially when compared to the direct costs to produce a bag of apheresis plasma at \$116.

The reality is that the various tests are performed on the whole blood prior to centrifugation occurring – it obviously makes economic sense to test only once rather than having to do so three times on each of the individual components.

Therefore, not to allocate part of the testing costs to each component does not reflect the economic reality of the cost to produce each component.

CADTH assumed in their model that the average cost of a bag of transfusion plasma in Canada is \$96. As this figure is based on their estimate of \$92, which for the above reasons is an artificially low number, the modelling performed by CADTH does not accurately measure the cost-effectiveness of Octaplas® versus Canadian FFP. It makes Octaplas® appear more expensive vis-à-vis Canadian FFP.

Further reinforcing the above theory is the fact that Canadian hospitals are “charged” \$175 for each bag of FFP ordered, as has been personally communicated to Octapharma by several transfusion specialists.

The conclusion of CADTH is that Octaplas® is more effective than FFP but more expensive. However, in our opinion, if all parameters of effectiveness had been considered (i.e. using a reduction in adverse events and their costs) and the real costs to the Canadian healthcare system of producing a bag of FFP (i.e. \$175) had been factored in by CADTH in their modelling, the conclusion would be that Octaplas® is not only more effective than FFP but also less expensive.

Octapharma will always push and collaborate for comprehensive decision- making processes regarding the safe and optimal use of blood components, particularly when these decision-making processes depart from a scientific, ethical and fair discussion.

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