Draft Questions for the Blood Products Advisory Committee

The applicant is proposing the use of Exjade as "indicated for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis). Exjade is indicated for both adult and pediatric patients aged 2 years and over".

The rationale for convening an Advisory Committee meeting for Exjade is based on the following considerations:

- Exjade is a New Molecular Entity
- Exjade has an Orphan Drug Designation
- Exjade is likely to be administered for indefinite periods of time
- The target indication for Exjade is a serious process that often leads to significant morbidity and premature death
- Current treatment for the proposed indication is often unsatisfactory
- The studies used an unvalidated method (superconducting quantum interference device, SQUID) for assessing endpoints in some patients
- Only one adequate and well-controlled trial (Study 0107) has been submitted in support of approval of the application
- The sponsor's acknowledges that the efficacy results in Studies 0107 and 0108 did not meet the prospective efficacy objectives
- Approval of Exjade would depend on analysis of subsets of patients in the trials, not on the entire populations
- There are significant safety concerns for treatment with Exjade that have been identified in the trials (renal, dermatological, hepatic, gastrointestinal, hematological, otological and ophthalmological)
- The number of patients exposed to Exjade is relatively small
- The studies are of insufficient length to evaluate the efficacy of Exjade in reducing morbidity and mortality in the target population
- The sponsor's recommendations for the initial and maintenance doses of Exjade are only partially supported by the results from the trials

As you review this background package, please consider the issues listed as they apply to the sponsor's application. We would then appreciate responses to the more specific questions posed below.

1. The standard measure of body iron stores is by assay of liver iron content (LIC). Reduction in LIC was used as the efficacy endpoint in Study 0107 (as well as in the non-pivotal trials). However, LIC may not represent an accurate state of the total body iron burden or the distribution of iron in other target organs.

Do you believe that a reduction in LIC is an acceptable efficacy endpoint? If not, what efficacy endpoint would you recommend?

2. The methods to detect LIC at baseline and changes in LIC during the trials were based on either liver biopsy or SQUID. The sponsor has provided data that indicate that the LIC measured by SQUID is approximately half of that measured by liver biopsy. In addition, there are significant differences among the LIC reported from the three SQUID sites used by the sponsor.

   Do you believe that the data from patients whose LIC was measured by SQUID should be used in the evaluation of the efficacy of Exjade?

   If not, do you believe that the study can be scientifically evaluated based upon the data from only those patients whose LIC was determined by liver biopsy?

3. The sponsor selected a non-inferiority margin of -15% for the comparison of Exjade to DFO. The effect of DFO on LIC has not been rigorously measured.

   Considering that the quantitative effect of DFO is not well known, how would you select an acceptable non-inferiority margin?

4. **Do the available data show a clinically significant effect of Exjade in decreasing iron burden in β-thalassemia patients? In any of the other populations studied?**

5. **If you feel that effectiveness of Exjade has been demonstrated for therapy in any indication, do you find that the available information is sufficient to direct initial and maintenance dosing? If yes, what dose regimen would you recommend?**

6. Preclinical and clinical studies indicate that Exjade has an adverse effect on renal function. The sponsor has presented clinical data that the renal effects were not progressive over a period of up to three years.

   In light of the likely requirement for long term use in the target population, do you believe that the risks of renal dysfunction outweigh the benefits to be derived from the drug?

7. There was an increase in serum transaminases in a small percent of patients treated with Exjade and two patients developed drug related hepatitis.

   In light of the likely requirement for long term use in the target population, do you believe that the risks of hepatic dysfunction outweigh the benefits to be derived from the drug?

8 Do you have any other safety concerns about Exjade?

9. Transfusional hemosiderosis is an orphan indication.

   Based on the available data, do you recommend approval of Exjade for treatment of β-thalassemia patients with transfusional hemosiderosis? Do you recommend approval of Exjade for treatment of any other patients with transfusional hemosiderosis?

10. **If you recommend approval of Exjade for any population, do you have any recommendations for post-marketing studies?**