

**BLA EFFICACY SUPPLEMENT MEDICAL REVIEW MEMO OF
SPONSOR'S RESPONSE TO COMPLETE REVIEW LETTER**

**EFFICACY SUPPLEMENT BASED ON POST MARKETING
COMMITMENT ROUTINE PROPHYLAXIS STUDY AND
SUPPORTIVE SAFETY AND PK DATA IN PEDIATRIC SUBJECTS
FROM PREVIOUSLY COMPLETED STUDIES**

STN # BL 125063/822 (Original BLA approved 25 July 2003)

SEE ALSO IND: -(b)(4)-

SPONSOR: Baxter Healthcare/Bioscience

**PRODUCT: Advate - Recombinant Antihemophilic Factor, Protein
Free Method (rAHF-PFM)**

REQUESTED NEW INDICATION:

**Routine prophylaxis to prevent or reduce the frequency of
bleeding episodes in adults and children (0-16 years) with
hemophilia A.**

CURRENT INDICATIONS:

- Control and prevention of bleeding episodes in adults and
children (0-16 years) with Hemophilia A**
- Perioperative management in adults and children (0-16 years)
with Hemophilia A**

RPMs: Mr. MARK SHIELDS, Ms. TILGHMAN

**SUBMISSION LETTER DATE: 21 NOVEMBER 2011, AMENDED 02
DEC 2011**

SUBMISSION CBER RECEIPT DATE: 21 NOVEMBER 2011

ACTION DUE DATE: 21 JANUARY 2011

REVIEWER: L. ROSS PIERCE, M.D., HFM-392

THROUGH: NISHA JAIN, MD., CHIEF, CRB, HFM-392

RECOMMENDATION:

Approve this efficacy supplement for a new indication for routine prophylaxis in children age 0-16 and adults.

Apprise the sponsor of the following typographical errors in the draft package insert, clean version submitted 13 December 2011, which may be corrected when submitting FPL and SPL:

- **Line 40: Remove the extra repeated “USP.”**
- **Line 46: Remove the 2 extra repeated “USPs.”**
- **Ensure consistency in spacing between sentences and between numbers and words as appropriate (i.e., an entry in Table 2 currently reads “(40-60International Units/kg^a). See also line 606.”**
- **Line 228: Remove the extra repeated “USP.”**

Reiterate to the sponsor that it is responsible for careful and diligent proof reading and appropriate correction of errors in all labeling submissions to FDA.

REVIEW

The sponsor was sent a CR letter on 27 Oct 2011 containing a single deficiency:

- **“The Office of Compliance and Biologics Quality, Division of Case Management is unable to complete the final approval action pending the review of the September 8-15, 2011 inspection of your Switzerland facility.**

In a memo dated 28 Nov 2011 and archived in the EDR, Shannon Aldrich of CBER/OCBQ wrote:

A recent Team Bio inspection of Baxter Healthcare Corporation located at 2000 Neuchatel, Switzerland (FEI #: 3002689389) was conducted September 8-15, 2011 and classified as Official Action Indicated (OAI). The inspection was reclassified to

Voluntary Action Indicated (VAI). Therefore, the office of Compliance and Biologics Quality, Division of Case Management does not object to the approval of this supplement.

In its labeling amendment submitted 13 December 2011, the sponsor has made all the changes to the draft package insert requested by FDA on 12 December 2011, however the sponsor still has not been consistent in the number of spaces separating sentences and it also has duplicated (or, in one case triplicated) the abbreviation "USP" in three instances in the HIGHLIGHTS section. The sponsor may correct these errors when submitting FPL/SPL.

In its labeling amendment submitted 02 Dec 2011, the sponsor had made all the changes to the draft package insert I requested in my final labeling review memo dated 01 October 2011, which were apparently communicated to the sponsor on 03 October 2011, except that the sponsor revised Table 3 in response to an FDA information request sent to the sponsor on 02 Dec 2011. That most recent information request asked the sponsor to use the following definition of adverse reaction (ADR) for the pooled analysis of ADRs in Table 3 in the ADVERSE REACTIONS section of the PI:

Any Adverse Event that began during an infusion or \leq 24 hours after the end of an infusion with the investigational product OR all Adverse Events assessed by the investigator or sponsor as related, probably related, or possibly related to investigational product OR Adverse Events for which the investigator's or sponsor's opinion of causality was missing or indeterminate.

I recommend the sponsor be asked to re-title Table 3 and to use a footnote to provide the operational definition of ADR used for this pooled analysis. OBRR commonly uses temporal association to help define ADRs in clinical trials lacking a randomized parallel placebo group, since there is no assurance in such cases that the sponsor's or investigator's assessments of causality of AEs is necessarily accurate. Limiting ADRs in such trials to the ADRs identified by the investigator may lead to an underestimation of the true ADR incidence, but no causality assessment method is wholly satisfactory in the absence of a gold standard. Given that many of the pooled Advate trials involved routine prophylaxis given up to 4 times weekly, the 24 hour time frame for temporal association of ADRs is considered to be more useful in helping to define possibly causally related ADRs, rather than the 72 hour time frame which OBRR has often employed for parenteral biologic products given at less frequent intervals. The sponsor submitted at FDA request the results of ADR analyses as tables using timeframes of temporal association of 24, 48, and 72 hours to help define ADRs (in addition to ADRs consisting of AEs already identified as at least possibly related according to the investigator or the sponsor).

Percent of AEs classified as ADRs among 234 subjects evaluated in 5 completed PTP and 1 ongoing PUP study as of Mar 2006 using 24, 48, and 72 hour time windows for temporal association (in addition to those AEs already classified as at least possibly related by the investigator or sponsor)

Time Window for Temporal Association	ADRs/AEs (ADRs as % of AEs)
24 hrs	1308/2507 (52.2%)
48 hrs	1798/2507 (71.7%)
72 hrs	1974/2507 (95.8%)

Qualitatively, the types of ADRs reported using the above 3 time frames for temporal association were quite similar.

The CMC reviewer has reviewed the DESCRIPTION and HOW SUPPLIED sections of the attached edited draft PI.

The medical reviewer and clinical pharmacology reviewer of Supplement 917 have verified the information in the CLINICAL STUDIES section of the PI relating to the PK and safety study comparing 2 mL and 5 mL reconstitution volumes, which was not the subject of this PAS /822.

The attached edited version of the sponsor's draft PI submitted 02 Dec 2011 reflects edits agreed to by Dr. Landow, Dr. T. Lee, Dr. Ze Peng, and myself in a meeting held 06 Dec 2011.