



**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research**

MEMORANDUM

Date: 23 July 2015

From: Wambui Chege, MD
Medical Officer, Pharmacovigilance Branch

Re: STN 125555\0

Through: Patricia Rohan, MD
Acting Branch Chief, Pharmacovigilance Branch

Christopher Jankosky, MD, MPH
Acting Deputy Director, Division of Epidemiology

Product: Nuwiq[®] (simoctocog alfa), [Antihemophilic Factor (Recombinant) plasma/albumin free]

Subject: Interim Post-market Safety Review
Action Due Date extended from 5Jun2015 to 4Sep2015
Major Amendment to Original Biologics License Application

Sponsor: Octapharma

1. INTRODUCTION

On 5Jun2014, Octapharma submitted an original Biologics License Application (BLA, 125555/0) to the Food and Drug Administration (FDA) for Nuwiq (simoctocog alfa) – a B-domain deleted recombinant Factor VIII (BDDrFVIII) product synthesized in Human Embryonic Kidney (HEK) cells and without the use of human serum or other animal-derived components. At that time, the sponsor's proposed indication was for use in the control and prevention of bleeding episodes (including during and after surgery) in adults and children with Hemophilia A.¹ Octapharma did not initially request an indication for use in routine prophylaxis.

On 4May2015, at the Late Cycle Meeting with the sponsor, FDA raised two substantive issues.² First, FDA noted that use for prevention of bleeding is considered separate and distinct from an indication for routine prophylaxis, and that although data had been provided to support an indication for routine prophylaxis, Octapharma had not explicitly requested the prophylaxis indication. In addition, data submitted by Octapharma to support the prophylaxis indication was not provided in analysis-ready SAS datasets to permit statistical evaluation of the data. Second, FDA requested clarification regarding data for validation of the (b) (4) method used to (b) (4) drug product. Discrepancies between FDA's and Octapharma's (b) (4) results prompted FDA to request two PMCs to resolve the issue – one PMC to validate the current (b) (4) method, and a second PMC to evaluate and consider a new (b) (4) method which has been found by FDA to be accurate and reliable for this product.

In response to the Late Cycle Meeting, Octapharma acknowledged their intention to request an indication for use in routine prophylaxis and agreed to submit the requested clinical datasets to FDA.³ Octapharma also committed to both PMCs involving the (b) (4) method.⁴

FDA deemed the clinical data subsequently submitted on 8May2015 (STN 125555/0.43) a Major Amendment, extending the review period with a new action due date of 4Sep2015.

2. OBJECTIVE

Safety related information for Nuwiq and the sponsor's proposed Pharmacovigilance Plan (PVP) were submitted with the original BLA and have previously been reviewed by the Division of Epidemiology (DE) in the Office of Biostatistics and Epidemiology (OBE) in a memorandum dated 13Apr2015.⁵ The DE/OBE safety review agreed with the sponsor's proposed postmarketing surveillance and with the post-approval studies listed in the PVP. In addition, at that time, the available safety data did not substantiate a need for a post-marketing requirement (PMR) study or a Risk Evaluation and Mitigation Strategy (REMS).

Shortly after submission of the original BLA to FDA, the product was licensed in several foreign countries. Nuwiq was first approved in the European Union (EU) on 22Jul2014 and was subsequently approved in Canada and Australia on 23Oct2014 and 5Nov2014, respectively. As a result, the sponsor compiled the first Periodic Safety Update Report (PSUR) describing postmarketing safety data from use of the product in the first four months following licensure in these foreign markets.⁶ The first PSUR was submitted to FDA in support of the BLA for Nuwiq, as part of the safety-related information available for the product and was reviewed by DE/OBE with no safety concerns identified.

Following the major amendment, the sponsor has compiled and submitted a second PSUR for Nuwiq.⁷ The objective of this memorandum is to review the safety data submitted in the second PSUR. This memorandum will function as an addendum to DE/OBE's prior review memorandum dated 13Apr2015.⁵

3. REVIEW OF INTERIM SAFETY DATA

On 30Apr2015, Octapharma submitted the second PSUR for Nuwiq to FDA for review. The PSUR has been reviewed in detail with relevant findings summarized below in an established OBE/DE format.

3.1 Review Period

The PSUR covers the four month period from 01-Dec-2014 to 30-Mar-2015.

3.2 Market Authorizations

The product continues to be licensed in the EU, Canada and Australia. The sponsor reports that no additional market authorizations have been issued within the review period.

3.3 Distribution Data and Estimates of Patient Exposure

The sponsor reports that cumulatively, 135 patients received a total of 16,203 infusions with Nuwiq in the completed interventional trials. In addition, four clinical trials with 187 patients enrolled are currently ongoing.

Between the first launch of Nuwiq (Oct-2014) and 30-Mar-2015, approximately (b) (4) of Nuwiq were sold worldwide. Assuming an average prophylactic dose of 30 IU/kg body weight and an average body weight of 50 kg this corresponds to (b) (4) administrations.

3.4 Changes to the Company Core Data Sheet

The sponsor reports no changes to the Company Core Safety Information (CCSI).

3.5 Regulatory Actions

No actions relating to the investigational use of Nuwiq or the marketing experience with the product were taken by regulatory authorities or by the marketing authorization holder.

3.6 Adverse Event Reporting

The sponsor reports that no spontaneous individual case safety reports (ICSRs) for Nuwiq have been received since the date of initial licensure. Serious adverse events reported from ongoing clinical trials for Nuwiq have been analyzed by the sponsor and are summarized in Table 1 below. No deaths have been reported.

Table 1. Summary of Serious Adverse Events Reported Between 01-Dec-2014 and 30-Mar-2015 from Ongoing Clinical Trials of Nuwiq

MedDRA System Organ Class	Total No. of Events	
MedDRA Preferred Term	Related	Unrelated
Infections and infestations	-	4
Device related infection	-	1
Acute tonsillitis	-	1
Lower respiratory tract infection	-	1
Upper respiratory tract infection	-	1
Psychiatric disorders	-	1
Depression suicidal	-	1
Nervous system disorders	-	2
Hepatic encephalopathy	-	1
Status epilepticus	-	1
Hepatobiliary disorders	-	1
Hepatic cirrhosis	-	1

Musculoskeletal and connective tissue disorders	-	1
Haemarthrosis	-	1
Injury, poisoning and procedural complications	-	3
Head injury	-	2
Traumatic fracture	-	1
TOTAL	0	12

3.7 New Safety Issues or Updates of Known Safety Issues

None.

3.8 Overall Assessment of Risk-Benefit Balance

The sponsor concludes that Nuwiq continues to offer a positive benefit-risk ratio.

4. CONCLUSION

The paucity of postmarketing safety data likely reflects the recent licensure of the product and the short period under review. In addition, while it is difficult to estimate patient exposure, the available data suggest that relatively few patients have been exposed to Nuwiq to date. The available adverse event reports list PTs that likely result from the underlying disorder and do not suggest a clinical syndrome attributable to use of the product (Table 1). At this time, review of the information included in the PSUR do not indicate any new safety concerns and OBE/DE continues to agree with the sponsor's proposed postmarketing surveillance and with the post-approval studies listed in the PVP contained in the original BLA submission.

¹ Octapharma. Nuwiq Draft Labeling Text. 5Jun2015 eCTD 125555/0.0

² FDA. Nuwiq Late Cycle Meeting Summary 29May2015 125555/0

³ Octapharma. Nuwiq. Amendment #44 Response to FDA information request dated May 5, 2015 eCTD 125555/0.43

⁴ Octapharma. Nuwiq. Amendment #45 Response to FDA information request dated May 8, 2015 eCTD 125555/0.44

⁵ FDA. Chege, W OBE/DE Pharmacovigilance Plan Review Memo. 13Apr2015 125555/0

⁶ Octapharma. Periodic Safety Update Report No 1a. 22-Dec-2014 120day Safety Report for 04-Aug-2014 to 30-Nov-2014 eCTD 125555/0.15

⁷ Octapharma. Amendment #40 Periodic Safety Update Report No 2. 28-Apr-2015 Safety Report for 01-Dec-2014 to 30-Mar-2015 eCTD 125555/0, seq 0040