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

MEMORANDUM

To:	Craig Zinderman, MD, MPH Acting Director, Division of Epidemiology (DE) Associate Director for Product Safety, DE Office of Biostatistics and Epidemiology (OBE), Center for Biologics Evaluation and Research (CBER)
Through:	Meghna Alimchandani, MD Associate Director for Medical Policy, OBE, CBER
From:	Wambui Chege, MD Team Lead, Medical Officer Pharmacovigilance Branch, DE, OBE, CBER
Subject:	Safety and Utilization Review for the Pediatric Advisory Committee
Applicant:	Octapharma
Product:	Nuwiq (simoctocog alfa)
STN:	125555
Indication:	For use in adults and children with Hemophilia A for: On-demand treatment and control of bleeding episodes, Perioperative management of bleeding, and Routine prophylaxis to reduce the frequency of bleeding episodes
Meeting Date:	Pediatric Advisory Committee Meeting, September 2019

Contents

1 INTRODUCTION

1.1 Objective

This memorandum for the Pediatric Advisory Committee (PAC) presents a comprehensive review of the postmarketing pediatric safety covering a period including 18 months following the approval in accordance with Section 505B (i) (1) of the Food and Drug Cosmetic Act [21 U.S.C. §355c]. The trigger for this pediatric postmarketing safety review was the approval of Nuwiq (simoctocog alfa) on 04Sep2015.

This memorandum documents FDA's complete evaluation, including review of adverse event reports in passive surveillance data, periodic safety reports from the manufacturer, data mining, and a review of the published literature.

1.2 Product Description

Nuwiq is a B-domain deleted recombinant Factor VIII (BDD-rFVIII) product synthesized in Human Embryonic Kidney (HEK) cells and without the use of human serum or other animal-derived components.

1.3 Regulatory History

Nuwiq was approved in the U.S. on 04Sep2015, for use in adults and children with Hemophilia A for:

- On-demand treatment and control of bleeding episodes
- Perioperative management of bleeding
- Routine prophylaxis to reduce the frequency of bleeding episodes

Nuwiq is manufactured by Octapharma.

2 MATERIALS REVIEWED

- FDA Adverse Events Reporting System (FAERS)
  - FAERS reports for Nuwiq for dates 04Sep2015 to 31Mar2019
- Manufacturer's Submissions
  - Nuwiq U.S. package insert, dated 07Jul2017 (125555/76)
  - Periodic Safety Update Reports (PSURs) covering the period from 04Sep2015 to 31Mar2019
  - Letter regarding dose distribution data, received 19Jun2019 (125555/141)
  - Risk Management Plan, No. 10, dated 07Dec2017 (125555/147)
- FDA Documents
  - Nuwiq Approval Letter, dated 04Sep2015
  - Division of Epidemiology Pharmacovigilance Plan Review Memorandum, dated 06May2015
- Publications

3 LABEL CHANGES IN REVIEW PERIOD

There have been no label changes related to safety concerns for Nuwiq since licensure.

4 PRODUCT UTILIZATION DATA

Octapharma has provided distribution data for the U.S. and worldwide for the period from 04Sep2015 to 31Mar2019.

Table 1: Distribution data for Nuwiq in the U.S. and Worldwide 04Sep2015 to 31Mar2019

Patient Age Group	U.S. Distribution Data (IU)	Worldwide Distribution Data (IU)
≤18 years	(b) (4)	(b) (4)
>18 years	(b) (4)	(b) (4)
All	(b) (4)	(b) (4)

Octapharma indicates that the estimates of use in U.S. children and adults are derived from estimates of the proportion of patients in each age group according to the 2017 World Federation of Hemophilia Annual Global Survey.[1] These estimates were provided by the manufacturer for FDA review. Distribution data is protected as confidential commercial information and may require redaction from this review.

Using distribution data provided by the sponsor, U.S. patient exposure to Nuwiq may be estimated as follows: Data from the Hemophilia Surveillance System established by the U.S. Center for Disease Control and Prevention (CDC), indicate that the prevalence and incidence of hemophilia A in the U.S. can be estimated at 10.5 per 100,000 males and 1 in 6,410 live male births.[2,3] Using this data, the proportion of incident cases or previously untreated patients (PUPs) can be calculated as approximately 2.6% of all U.S. male hemophiliacs and that of previously treated patients (PTPs) as 97.4%. A meta-analysis of studies on the mean annual consumption of recombinant FVIII by PTPs and PUPs estimates 148,700 IU consumed annually per PTP and 48,600 IU per PUP.[3] Applying these rates to the amount distributed in the U.S., the number of patients exposed to Nuwiq in the U.S. from the time of FDA licensure on 4Sep2015 to 31Mar2019 can be estimated as (b) (4) PUPs and (b) (4) PTPs for a total of (b) (4) patients.

It is important to note that this estimate of the number of patients treated is at best an approximation since all the distributed doses may not have been administered to patients. In addition, other factors such as off-label use and dose adjustment at the discretion of the treating physician can affect this estimation. Also of note, data used in

[1] World Federation of Hemophilia Report on the Annual Global Survey 2017. October 2018. Available at http://www1.wfh.org/publications/files/pdf-1714.pdf

[2] Soucie JM, Evatt B, Jackson D *et al* Occurrence of Hemophilia in the United States *Am J Hem* (1998) 59:288-294

[3] Ewenstein BM, Gomperts ED, Pearson S *et al* Inhibitor development in patients receiving recombinant factor VIII (Recombinate rAHF/Bioclate®): a prospective pharmacovigilance study. *Hemophilia* (2004) 10:491-498

the calculation of this patient estimate use multiple sources including both U.S. and international data.

5 PHARMACOVIGILANCE PLAN AND POSTMARKETING STUDIES

5.1 Pharmacovigilance Plan (PVP)

The manufacturer's current Risk Management Plan for Nuwiq is Version 10, dated 07Dec2017. Tables 2, 3 and 4 describe the identified risks, potential risks and missing information for Nuwiq, as well as the planned activities to address each safety concern. Postmarketing studies listed as planned activities in the PVP are reviewed in detail in section 5.2 below.

Table 2: Important Identified Risks and Planned Pharmacovigilance Actions for Nuwiq[4]

Safety Concern	Planned Activity
Inhibitor development (antibodies against rhFVIII)	GENA-05, GENA-13, GENA-15, GENA-99, EUHASS Routine Pharmacovigilance
Hypersensitivity including anaphylaxis	GENA-13, GENA-99, EUHASS Routine Pharmacovigilance
Cardiovascular events	Routine Pharmacovigilance

EUHASS=European Haemophilia Safety Surveillance

Table 3: Important Potential Risks and Planned Pharmacovigilance Actions for Nuwiq[4]

Safety Concern	Planned Activity
Thromboembolic events	GENA-99, EUHASS Routine Pharmacovigilance
Medication errors including in home setting	GENA-99, EUHASS Routine Pharmacovigilance

EUHASS=European Haemophilia Safety Surveillance

[4] Octapharma. Nuwiq, Risk Management Plan, Version 10 07Dec2017. eCTD 125555/147.

Table 4: Missing Information and Planned Pharmacovigilance Actions for Nuwiq[4]

Safety Concern	Planned Activity
Safety in Previously Untreated Patients (PUPs)	GENA-05 Routine Pharmacovigilance
Use in children <2yo	GENA-05, GENA-99 Routine Pharmacovigilance
Safety in pregnant or breastfeeding women	Routine Pharmacovigilance
Immune tolerance induction (ITI)	GENA-05 Routine Pharmacovigilance

Nuwiq does not have a requirement for a postmarketing safety study under the FDA Amendments Act (FDAAA) or a Risk Evaluation and Mitigation Strategy (REMS).

5.2 Postmarketing Studies

The 4 studies listed in the PVP are postmarketing commitments (PMCs) and are listed on the approval letter for Nuwiq.[5] The 4 PMCs including approximate study milestones are listed below.

1. **GENA-05 – PUPs Study**: Evaluation of immunogenicity, efficacy and safety of Antihemophilic Factor (Recombinant) in previously untreated patients (PUPs).
   Study completion date: November 30, 2018
   Final Report Submission date: July 01, 2019[6]
2. **GENA-13 – Pediatric Extension Study**: Evaluation of long-term immunogenicity, tolerability, and efficacy of Antihemophilic Factor (Recombinant) in previously treated children.
   Study/trial completion date: June 30, 2016
   Final Report Submission date: November 30, 2016
3. **GENA-15 – PUPs Extension Study**: Extension study for patients who completed GENA-05 to Investigate Immunogenicity, Efficacy and Safety of Treatment with Nuwiq.
   Study completion date: November 30, 2018
   Final Report Submission date: November 30, 2019[6]
4. **GENA-99 – Long-term Observational Trial**: Post-licensure trial to document long-term immunogenicity, safety, and efficacy of Antihemophilic Factor (Recombinant) in patients treated in normal clinical practice.
   Study/trial completion date: June 30, 2019
   Final Report Submission date: March 31, 2020

Of the 4 PMCs listed in the PVP, two studies – GENA-13, the Pediatric Extension Study and GENA-05, the PUPs Study – are complete and the final study reports have been

[5] FDA. Nuwiq. Approval letter 4Sep2015 eCTD 125555/0
[6] Octapharma. Correspondence Re: PMR/PMC STN 125555 - study GENA-05 and GENA-15 30Apr2019 eCTD 125555 seq 154

submitted to FDA for review. The final study report for GENA-13, the Pediatric Extension Study has been reviewed in detail by FDA and safety related data from the study is summarized in Table 5 below. (b) (4)

Table 5. Summary of GENA-13 Pediatric Extension Study Final Report[7,8]

Study Title:	Clinical Study in Previously Treated Children with Severe Hemophilia A to Investigate the Long-Term Immunogenicity, Tolerability and Efficacy of Nuwiq
Study Design:	Prospective, open-label, uncontrolled, international, multi-center Phase 3b study
Eligibility criteria:	• Completion of Pediatric Trial GENA-03 • Voluntary written and signed consent • No development of FVIII inhibitors (≥0.6 BU) in GENA-03 • No severe liver or kidney disease (ALT and AST levels >5 times of upper limit of normal, creatinine >1.2 µmol/dL)
No. of subjects:	49
1˚ Objective:	• To determine the long-term immunogenicity and tolerability of Nuwiq in previously treated children with severe Hemophilia A.
2˚ Objectives:	• To determine the long-term efficacy of Nuwiq in the prophylaxis and in the treatment of breakthrough bleeding episodes, and in surgical prophylaxis in previously treated children with severe Hemophilia A.
Safety Related Results:	• 21 patients experienced a total of 30 SAEs • 1 SAE was a death due to multiorgan failure following a car accident • The sponsor reports that 13 SAEs in 11 patients were related to the patients' underlying condition, i.e., device-related events (N=8), hematuria (N=2), hematoma (N=1), hemarthrosis (N=1), and synoviorthesis (N=1) • Other SAEs included urinary tract infection (N=3), pyrexia (N=2), abdominal pain (N=1), abdominal pain upper (N=1), appendicitis (N=1), head injury (N=1), headache (N=1), hernia (N=1), ingrowing nail (N=1), osteoma (N=1), pharyngitis (N=1), pneumonia (N=1), renal colic (N=1) • No subjects developed FVIII inhibitors

[7] Octapharma. Clinical Study Protocol. Clinical Study in Previously Treated Children with Severe Haemophilia A to Investigate the Long-Term Immunogenicity, Tolerability and Efficacy of Human-cl. rhFVIII GENA-13, version 05(Protocol version 01 with Amendment 03 and 05 incorporated) 29Jul2015 eCTD 125555/3.0 and 13722/0.47

[8] Octapharma. Clinical Study Report. Clinical Study in Previously Treated Children with Severe Haemophilia A to Investigate the Long-Term Immunogenicity, Tolerability and Efficacy of Human-cl rhFVIII 22Nov2016 eCTD 125555/50

The final study report for GENA-05, the PUPs Study was recently submitted to FDA and is also currently under review (125555/150). Interim data have previously been provided for GENA-05, the PUPs Trial, from a pre-planned interim analysis conducted after 50 PUPs had reached at least 50 exposure days (ED). The safety related results from these interim data are summarized in Table 6 below.

Table 6. Summary of GENA-05 PUPs Study Interim Results[9,10]

Study Title:	Immunogenicity, efficacy and safety of treatment with Nuwiq in PUPs with severe HA
Study Design:	Prospective, open label, non-controlled, multi-center Phase III study
Eligibility criteria:	PUPs with severe hemophilia A (FVIII:C <1%) No age restrictions
No. of subjects:	66 as of May2016 110 as of Mar2019
1˚ Objective:	Immunogenicity
2˚ Objectives:	Efficacy of Prophylactic treatment, Treatment of bleeding episodes and Surgical prophylaxis Safety and tolerability
Safety Related Results (as of May 2016):	• High-titre (HT) inhibitors developed in 8 of 66 patients for a cumulative incidence 12.8% (95%CI: 4.5%, 21.2%). Five patients developed low-titre inhibitors of which 4 were transient. The total cumulative incidence for all inhibitors was 20.8% (95% CI: 10.7%, 31.0%) • Other reported AEs include 1 patient experienced allergic reactions (N=3), 1 patient who each experienced mild fever (N=1), and 1 patient who experienced rash (N=1) • No thromboembolisms or severe allergic reactions were recorded

6 ADVERSE EVENT REVIEW

6.1 Methods

The FDA Adverse Event Reporting System (FAERS) was queried for adverse event reports following the use of Nuwiq between 4Sep2015 (initial approval) and 31Mar2019. FAERS stores postmarketing adverse events and medication errors submitted to FDA for all approved drug and therapeutic biologic products. These reports originate from a variety of sources, including healthcare providers, consumers, and manufacturers. Spontaneous surveillance systems such as FAERS are subject to many limitations, including variable report quality and accuracy, inadequate data regarding the numbers of doses administered, and lack of direct and unbiased comparison groups. Reports in FAERS may not be medically confirmed and are not verified by FDA. FDA does not

[9] Liesner RJ, Abashidze M, Aleinikova O *et al*. Immunogenicity, efficacy and safety of Nuwiq®(human-cl rhFVIII) in previously untreated patients with severe haemophilia A-Interim results from the NuProtect Study. *Haemophilia* 2018;24:211–220.
[10] Octapharma. SUR No.7 18Mar2019 eCTD 125555/136

receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Also, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven.

6.2 Results

The results of the FAERS search of adverse event reports for Nuwiq during the review period are listed in Table 7 below. There were 12 U.S. and 7 foreign reports.

Table 7. Adverse event reports for Nuwiq in FAERS between 04Sep2015 and 31Mar2019

Age	Serious non-fatal, US	Serious Non-fatal, Foreign	Deaths, US	Deaths, Foreign	Non-Serious, US	Non-Serious Foreign	Total, US	Total, Foreign
<18 years	1	6	0	0	4	0	5	6
≥18 years	3	0	0	1	3	0	6	1
Unknown	0	0	0	0	1	0	1	0
All ages	4	6	0	1	8	0	12	7

Note: Serious non-fatal adverse events include life-threatening events, hospitalization, prolongation of hospitalization, congenital anomaly, or significant disability, and otherwise medically important conditions (OMIC).

6.2.1 Deaths

There were no pediatric deaths reported. The single report of adult death was reviewed and is summarized below.

A 49-year-old male was on Nuwiq for hemophilia A. The patient also had a past medical history of HIV infection, Hepatitis C, liver cirrhosis with esophageal varices and pulmonary arterial hypertension. He was admitted with chest pain and on (b) (6) an angiography scan revealed multiple pulmonary emboli for which anticoagulation was started. The patient was also found to have an intrahepatic lesion, later diagnosed as hepatocellular carcinoma with right portal vein thrombosis, perihilar adenopathy and tumor invasion of the middle hepatic vein and inferior vena cava. On (b) (6) the patient died as a result of meningeal haemorrhage. An autopsy was not performed.

There are multiple potential diagnoses and interventions that may have contributed to this fatal episode of meningeal hemorrhage. The role of Nuwiq, if any, in this report of death, is unclear.

6.2.2 Serious Non-fatal Reports

During the reporting period, there were 10 serious, non-fatal reports; 7 of which involved pediatric patients and are summarized below.

A 10-year-old male in Italy, with severe hemophilia A was switched to Nuwiq for prophylaxis. The patient developed ecchymoses and petechiae. The frequency of Nuwiq was increased and symptoms increased. The medication was switched back to the previous factor VIII and all the manifestations disappeared.

A 12-month-old male patient in Germany on Nuwiq for severe hemophilia A, had a medical history of epilepsy and intracranial haemorrhage. in 2015. After an infusion of Nuwiq, the patient was febrile, shivering, pale and cyanotic. He was hospitalized for a Staphylococcus epidermidis infection.

A 21-month-old male in Sweden presented with inhibitors and started on immune tolerance induction (ITI) therapy with Nuwiq. A few minutes after the infusion was complete he experienced anaphylaxis with circulatory shock, tachycardia, hypotension, decreased consciousness and hypoxia thought to be due to a port-a-cath infection. The patient recovered with treatment. The patient received two additional infusions with Nuwiq and developed rash after each infusion without circulatory collapse. The Nuwiq ITI therapy was withdrawn.

A 2-year-old male in Switzerland with severe hemophilia A and hemarthrosis switched from Haemate to Nuwiq. Three days after receipt of Nuwiq, the patient was admitted to the hospital with bilateral periorbital edema and was diagnosed with nephrotic syndrome. He received steroids and continued on Nuwiq with no issues.

A 3-year-old male in France was on Nuwiq for hemophilia A. He was hospitalized for management of acute lymphocytic leukemia, fever and abdominal pain and was hospitalized.

A 16-year-old male in France was on Nuwiq for prophylaxis. He experienced a hematoma of the left tibia and a right ankle pain and was sent to the emergency room. At the time of this report the patient had not recovered from the hematoma.

A 4-year-old male in the United States received Nuwiq for hemophilia A and was taken to the emergency room due to fever and other medical issues. No further information was provided.

The most frequently reported MedDRA preferred term (PT) for serious non-fatal pediatric reports was Pyrexia (n=3) with a total of 24 other PTs appearing one time each. Of the 25 PTs, 3 of the PTs are listed in the product label - Adverse drug reaction, Anaphylactic reaction and Rash. Several unlabeled PTs such as Arthralgia and Haematoma are confounded by indication. Other unlabeled PTs describe unrelated diagnoses or non-specific events.

6.2.3 Non-serious Reports

During the reporting period, there were 8 non-serious reports; 4 of which involved pediatric patients. All PTs for the 8 non-serious reports received for all ages are listed in Table 8 below.

Table 8: All preferred terms (PTs) for non-serious reports among all ages

Preferred Term (PT)	Number of Reports	Label Status
Abnormal Behaviour	1	Unlabeled
Arthralgia	1	Unlabeled
Arthropathy	1	Unlabeled
Coagulopathy	1	Unlabeled
Contusion	1	Unlabeled
Education Problem	1	Unlabeled
Elbow Deformity	1	Unlabeled
Enzyme Inhibition	1	Unlabeled
Hot Flush	1	Unlabeled
Mental Disorder	1	Unlabeled
Muscle Haemorrhage	1	Labeled
Personality Change	1	Unlabeled
Pruritus	1	Labeled
Shoulder Deformity	1	Unlabeled

Most unlabeled PTs are confounded by indication. Other unlabeled PTs describe unrelated diagnoses or non-specific events.

6.3 Data mining

Data mining was performed to evaluate whether any events following the use of Nuwiq were disproportionally reported compared to all other products in the FAERS database. Data mining covers the entire postmarketing period for this product, from initial licensure through the data lock point for the data mining analysis of 09Jun2019.

Disproportionality alerts do not, by themselves, demonstrate causal associations; rather, they may serve as a signal for further investigation. A query of Empirica Signal using the Product (S) run identified no preferred terms (PTs) with a disproportional reporting alert. A disproportional reporting alert is defined as an EB05>2 where the EB05 refers to the lower bound of the 90% confidence interval around the Empiric Bayes Geometric Mean.

6.4 Periodic safety reports

The manufacturer's postmarketing periodic safety reports for Nuwiq covering the surveillance period were reviewed. The adverse events reported were consistent with those seen in FAERS. One signal was described by the sponsor in a periodic safety report in the review period, and is described below.

In the Periodic Safety Update Report (PSUR) dated 20Sep2018, the sponsor reported an ongoing signal regarding the increased incidence of FVIII inhibitors in PUPs treated with rFVIII compared to plasma-derived products.[11] This finding was published following a review of data from a cohort of patients in FranceCoag, a national pharmacosurveillance network for French patients with inherited coagulopathies.[12] Of note, none of the patients in the study received Nuwiq. The European Medicines Agency (EMA) reviewed the data and concluded that "no regulatory action was warranted at this stage."[13] Following the EMA's findings, Octapharma closed the signal, and plans continued "[m]onitoring of newly emerging data on the incidence of inhibitors in PUPs in the PSURs."[14] No additional safety issues were identified, and no actions were taken by the sponsor for safety reasons.

7 LITERATURE REVIEW

A search of the U.S. National Library of Medicine's PubMed.gov database on 12Jun2019, for peer-reviewed literature, with the search term "Nuwiq" retrieved 13 articles. The articles were reviewed, and the safety conclusions are listed in the table below. No new safety concerns for Nuwiq were identified in these articles.

Article	Authors' Safety Conclusion
Estimation of Nuwiq® (simoctocog alfa) activity using one-stage and chromogenic assays-Results from an international comparative field study. Tiefenbacher S, Albisetti M, Baker P *et al* *Haemophilia*. 2019 May 20. doi: 10.1111/hae.13763. [Epub ahead of print]	Both assays are suitable for the measurement of FVIII activity of Nuwiq in routine laboratory practice, without the need for a product-specific reference standard.

[11] Octapharma. Nuwiq Periodic Safety Update Report (PSUR) No.9, 20Sep2018 eCTD 125555/118
[12] Calvez T, Chambost H, d'Oiron R, et al Analyses of the FranceCoag cohort support differences in immunogenicity among one plasma-derived and two recombinant factor VIII brands in boys with severe hemophilia A. *Haematologica*. 2018 Jan; 103(1):179-89.
[13] European Medicines Agency. 8Mar2018 EMA/PRAC/218598/2018. Inspections, Human Medicines Pharmacovigilance and Committees Division, Pharmacovigilance Risk Assessment Committee (PRAC) Minutes of the meeting on 05-08 February 2018. Available at https://www.ema.europa.eu/en/documents/minutes/minutes-prac-meeting-5-8-february-2018_en.pdf
[14] Octapharma. Nuwiq Periodic Safety Update Report (PSUR) No.7, 18Mar2019 eCTD 125555/136

Article	Authors' Safety Conclusion
Individual thrombin generation and spontaneous bleeding rate during personalized prophylaxis with Nuwiq® (human-cl rhFVIII) in previously treated patients with severe haemophilia A. Dargaud Y, Negrier C, Rusen L *et al* *Haemophilia*. 2018 Jul;24(4):619-627. doi: 10.1111/hae.13493. Epub 2018 May 31.	GENA-21 was a prospective, open-label, phase IIIb study investigating the safety and efficacy of Nuwiq. In previously treated adults with severe haemophilia A and reduced thrombin generation, increased frequency of spontaneous bleeding was observed irrespective of trough FVIII levels. Thus, personalized prophylaxis should take into account variables other than FVIII activity.
Long-term tolerability, immunogenicity and efficacy of Nuwiq® (human-cl rhFVIII) in children with severe haemophilia A. Klukowska A, Szczepański T, Vdovin V *et al* *Haemophilia*. 2018 Jul;24(4):595-603. doi: 10.1111/hae.13460. Epub 2018 Mar 26	GENA-13 was a study of long-term tolerability, immunogenicity and efficacy of Nuwiq prophylaxis in children. Long-term treatment with Nuwiq for the prevention of bleeds in children with severe haemophilia A was well tolerated and effective.
Efficacy and safety of Nuwiq® (human-cl rhFVIII) in patients with severe haemophilia A undergoing surgical procedures. Zozulya N, Kessler CM, Klukowska A *et al* *Haemophilia*. 2018 Jan;24(1):70-76. doi: 10.1111/hae.13351. Epub 2017 Oct 19	This pooled analysis shows that Nuwiq was safe and efficacious in maintaining haemostasis during and after major and minor surgical procedures in PTPs with severe haemophilia A. There were no serious treatment-related adverse events, and none of the patients developed FVIII inhibitors.
Immunogenicity, efficacy and safety of Nuwiq® (human-cl rhFVIII) in previously untreated patients with severe haemophilia A-Interim results from the NuProtect Study. Liesner RJ, Abashidze M, Aleinikova O *et al* *Haemophilia*. 2018 Mar;24(2):211-220. doi: 10.1111/hae.13320. Epub 2017 Aug 16.	GENA-05 is a study of immunogenicity, efficacy and safety of Nuwiq in PUPs with severe haemophilia A. Interim data from this study show a cumulative incidence of 12.8% for high titer inhibitors and evidence of both efficacy and tolerability in PUPs treated with Nuwiq .

Article	Authors' Safety Conclusion
PK-guided personalized prophylaxis with Nuwiq® (human-cl rhFVIII) in adults with severe haemophilia A. Lissitchkov T, Rusen L, Georgiev P *et al* *Haemophilia*. 2017 Sep;23(5):697-704. doi: 10.1111/hae.13251. Epub 2017 Apr 27. Erratum in: *Haemophilia*. 2018 Jan;24(1):162.	GENA-21 is a trial to investigate the efficacy and safety of a personalized prophylaxis regimen in adult PTPs with severe hemophilia A. PK-guided personalized prophylaxis with Nuwiq provided bleeding protection and enabled the dosing interval to be extended to twice weekly or less in many patients and an overall dose reduction.
Efficacy and safety of a recombinant factor VIII produced from a human cell line (simoctocog alfa). Franchini M, Mannucci PM. *Expert Opin Drug Saf.* 2017 Mar;16(3):405-410. doi: 10.1080/14740338.2017.1285281. Epub 2017 Feb 1. Review	This review article describes the efficacy and safety of Nuwiq as presented in the results of the phase II and III clinical trials of PTPs and the interim data from the phase III trial on PUPs. The authors conclude that the available data document the high efficacy and safety profile of the product, which has the potential to reduce the inhibitor risk in PUPs with severe hemophilia A.
Pharmaceutical Approval Update. Gohil K. P T. 2015 Nov;40(11):726-74	Nuwiq is a novel addition to the treatments available for hemophilia A. Approval was based on studies that demonstrated significant efficacy and safety in terms of bleeding episodes.
Prophylaxis vs. on-demand treatment with Nuwiq(®) (Human-cl rhFVIII) in adults with severe haemophilia A. Tiede A, Oldenburg J, Lissitchkov T *et al* *Haemophilia*. 2016 May;22(3):374-80. doi: 10.1111/hae.12859. Epub 2015 Nov 19.	Prophylaxis with Nuwiq reduces recurrent bleeding in adult PTPs with severe haemophilia A and adds further supportive evidence for the benefits of prophylaxis in adults.

Article	Authors' Safety Conclusion
Novel, human cell line-derived recombinant factor VIII (Human-cl rhFVIII, Nuwiq®) in children with severe haemophilia A: efficacy, safety and pharmacokinetics. Klukowska A, Szczepański T, Vdovin V *et al* *Haemophilia*. 2016 Mar;22(2):232-239. doi: 10.1111/hae.12797. Epub 2015 Sep 14	GENA-03 was a prospective, open-label, multinational phase III study that evaluated the efficacy and safety of Nuwiq in PTPs with severe haemophilia A aged 2-12 years during standard prophylaxis. These results indicate that Nuwiq is effective for the prevention and treatment of bleeds in paediatric PTPs.
Development, upscaling and validation of the purification process for human-cl rhFVIII (Nuwiq®), a new generation recombinant factor VIII produced in a human cell-line. Winge S, Yderland L, Kannicht C *et al* *Protein Expr Purif*. 2015 Nov;115:165-75. doi: 10.1016/j.pep.2015.08.023. Epub 2015 Aug 28	The purification process involves one centrifugation, two filtration, five chromatography columns and two dedicated pathogen clearance steps (solvent/detergent treatment and 20 nm nanofiltration). The innovative purification process ensures a high-purity and high-quality product with a high pathogen safety margin.
Novel, human cell line-derived recombinant factor VIII (human-cl rhFVIII; Nuwiq®) in adults with severe haemophilia A: efficacy and safety. Lissitchkov T, Hampton K, von Depka M *et al* *Haemophilia*. 2016 Mar;22(2):225-231. doi: 10.1111/hae.12793. Epub 2015 Aug 28.	In adult PTPs Nuwiq is effective for the prevention and treatment of bleeds in adults with severe haemophilia A. No patients developed FVIII inhibitors and there were no treatment-related serious or severe adverse events.

Article	Authors' Safety Conclusion
Spotlight on the human factor: building a foundation for the future of haemophilia A management: report from a symposium on human recombinant FVIII at the World Federation of Hemophilia World Congress, Melbourne, Australia on 12 May 2014. Kessler C, Oldenburg J, Ettingshausen CE *et al* *Haemophilia*. 2015 Jan;21 Suppl 1:1-12. doi: 10.1111/hae.12582. Review.	This article reviews the results of the registration clinical trials for Nuwiq as well as the ongoing study in PUPs and the personalized prophylaxis study in PTPs.

8 CONCLUSION

This postmarketing pediatric safety review of passive surveillance adverse event reports, the sponsor's periodic safety reports, and the published literature for Nuwiq does not indicate any new safety concerns. The PAC review was initiated due to the initial FDA approval in both pediatric and adult patients. There were few adverse events reported in the pediatric age group (<18 years) during the review period and even fewer adverse events reported in adults. There were no reports of pediatric death. No unusual frequency, clusters, or other trends for adverse events were identified that would suggest a new safety concern.

9 RECOMMENDATIONS

FDA recommends continued routine safety monitoring of Nuwiq.