



Department of Health and Human Services
Public Health Service
United States Food and Drug Administration
Center for Biologics Evaluation and Research



Addendum Pharmacology / Toxicology Primary Discipline Review

To: File (Original BLA 125555/0)

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Subject: STN 125555/0 – Octapharma’s Original Biological License Application (BLA) for Nuwiq® antihemophilic factor, human recombinant beta domain deleted (codename rhFVIII-BDD)

Indication: Treatment for the control and prevention of bleeding episodes, including during and after surgery, in adults and children with Hemophilia A

This memorandum is an addendum to the final primary pharmacology and toxicology review based on the nonclinical program data included in the Original Biological License Application (BLA) for Octapharma’s Nuwiq® antihemophilic factor, human recombinant beta domain deleted (codename rhFVIII-BDD). Nuwiq is indicated for the control and prevention of bleeding episodes, including during and after surgery, in adults and children with Hemophilia A. From the toxicology and pharmacology reviewer’s perspective, this original biological application STN 125555/0 is recommended for approval; therefore, the final SBRA and labeling will become part of the action package for this BLA and documentation of their review is required.

Reviewer comments: The final recommendations from the previous nonclinical reviews to approve Nuwiq™ for its intended use and patient population have not changed. The nonclinical data submitted in the original BLA submission STN #125555/0 support that Nuwiq™ is reasonably safe for its intended use in the control and prevention of bleeding episodes, including during and after surgery, in adults and children with Hemophilia A. The nonclinical data that supported this decision are described in the respective section of the SBRA, below. The SBRA was submitted to OBRR senior management for their review, and their revisions of this section are included in this addendum. at a later date.

Official Summary Basis for Regulatory Action (SBRA)

4. Non-clinical Pharmacology/Toxicology

General Considerations

NUWIQ™ [Antihemophilic Factor (Recombinant), plasma/albumin free; rFVIII] was determined to be safe for its intended use as treatment for the control and prevention of bleeding episodes, including during and after surgery, in adults and children with congenital FVIII deficiency (Hemophilia A) based on Good Laboratory Practices (GLP)-compliant and non-GLP studies, and on its experimental clinical trials both within and outside of the United States. The safety and effectiveness of rFVIII were characterized in a

nonclinical program that included in vivo efficacy testing and induction of thrombogenesis by former-NUWIK™, as well as in vivo pharmacokinetics, local tolerability, and single and repeat-dose toxicity studies in FVIII-deficient (hemophilic) dogs, and in FVIII replete (i.e., wild-type) monkeys, rats, and rabbits. A risk assessment of the potential extractable and leachable components present in the rFVIII drug substance, as per the (b) (4) standards was also completed.

Previous experience with similar recombinant and plasma-derived FVIII products has demonstrated that the toxicities of exogenously administered FVIII are extensions of its pharmacologic activity, i.e. hypercoagulability of blood, thrombosis, and thromboembolus formation in treated animals and patients. Additional expected nonclinical findings are development of neutralizing and non-neutralizing antibodies directed against the human FVIII protein (i.e., immunogenicity), with the potential to cross-react and neutralize endogenous FVIII in wild-type animals and potential increase in inhibitor antibody titre levels.

Nonclinical Findings

Pharmacology

Nonclinical pharmacology studies with former-NUWIK™ were conducted in a canine model of Hemophilia B (i.e., dogs with a naturally occurring mutation/deletion of FVIII function), and in normal, FVIII-replete (i.e., wild-type) rats. Hemophilic dogs that had been tolerized to human FVIII were dosed intravenously with increasing doses of former-NUWIK™, another approved recombinant human FVIII product, or a marketed human plasma-derived FVIII concentrate in a cross-over study design. Dosing of hemophilic dogs with former-NUWIK™ at doses approximately equivalent to the human starting dose restored the ex vivo whole blood clotting time (WBCT) activity and activated partial thromboplastin times (aPTT) to within normal limits, and the results were comparable to those obtained following dosing with the two approved human FVIII products. There were no effects of former-NUWIK™ or the other FVIII preparations on the hematology profiles in the dogs as compared to prior to dosing (i.e., baseline), and no serious adverse effects or evidence of thrombogenicity were reported.

Secondary pharmacology studies with former-NUWIK™ in wild-type rats showed no elevations of ex vivo biomarkers of thrombosis (i.e., thrombin, thrombin-anti-thrombin complex, D-dimer and prothrombin fragments 1+2 formation) at doses up to 14-fold greater than the maximum NUWIK™ clinical dose. Biomarker results were similar to those achieved in rats dosed with the comparator groups of an approved recombinant human FVIII product, or a marketed human plasma-derived FVIII concentrate. No abnormal tissue pathology, and only sporadic evidence of in situ thrombosis with no apparent relationship in the incidence or severity to the FVIII dose level were observed on microscopic examination of lung and other tissues from rats dosed with rFVIII.

In summary, animal studies with rFVIII showed the expected pharmacologic (pro-coagulant) activity in a canine model of Hemophilia A, and the results were similar to those obtained with other approved human FVIII products. There was no evidence of undesirable secondary pharmacologic activity, i.e., thrombogenesis, in FVIII-replete rats dosed with rFVIII at dose levels up to 14-fold greater than the equivalent human NUWIK™ starting dose. These data were used as proof-of-concept to support the rationale for entering former-NUWIK™ into clinical trials, and to support the pharmacology section of the NUWIK™ BLA Package Insert (PI).

Pharmacokinetics

Pharmacokinetic studies with former-NUWIK™ were conducted concurrently with the pharmacology studies in the human FVIII-tolerized, Hemophilia A dogs described above, and FVIII activity was measured by both the one-stage clotting and chromogenic assays. With both assays, the PK profiles from hemophilic dogs dosed with former-NUWIK™ showed dose-dependent increases in all parameters measured, and were comparable to those obtained when the dogs were dosed with the approved, human recombinant FVIII comparator. Similar results were obtained in FVIII-replete, wild-type rats with former-

NUWIKTM and the two approved, human FVIII comparator products. A series of PK studies in FVIII-replete, wild-type rats and monkeys showed that the rFVIII product tested in the nonclinical safety program were comparable to those used in clinical trials, and that changes in manufacturing during the development program did not affect the critical PK parameters.

Toxicology

Overall, the nonclinical safety profile of rFVIII did not identify any unexpected findings or significant concerns in toxicity studies conducted in wild-type, FVIII-replete rats, rabbits, and (b) (4) monkeys. Monkeys were dosed with a single, intravenous injection of rFVIII at doses up to 125-fold greater than the clinical starting dose demonstrated no systemic or tissue pathologies. A repeat dose toxicity study with rFVIII was conducted in rats; animals were dosed daily for 28 days by bolus intravenous injection with rFVIII doses equal to, and up to 14-fold greater than the clinical starting dose. Although statistically significant differences in some measured parameters of toxicity were reported (e.g., hematology, prothrombin time and aPTT, serum chemistry and urinalysis), the findings were not consistent or dose-related between the rFVIII dose groups, and no corresponding histopathological findings were detected. The findings in the rFVIII dosed rats were comparable to those receiving an equivalent dose of either an approved, recombinant human FVIII product or a human plasma-derived FVIII concentrate as comparators, suggesting that the safety profile of NUWIKTM is similar to that of other, approved FVIII products. A repeat dose toxicity study with rFVIII was conducted in (b) (4) monkeys; animals were dosed daily for 28 days by bolus intravenous injection with rFVIII doses equal to, and up to 10-fold greater than the clinical starting dose. Although statistically significant differences in some measured parameters of toxicity were reported (e.g., hematology, prothrombin time and aPTT, serum chemistry and urinalysis), the findings were consistent and dose-related between the rFVIII dose groups, and corresponding histopathological findings were detected. Animal findings for toxicity studies were expected and consistent based on exaggerated pharmacologic effects for recombinant and plasma derived FVIII products. Dermal toxicity and local tolerance studies conducted in rabbits administered the clinical dose of rFVIII revealed acceptable levels of inflammation and edema at the injection site.

There were no animal studies for carcinogenicity, in vivo mutagenicity, fertility, reproductive toxicity or teratogenicity conducted with rFVIII. As rFVIII is a recombinant, human protein, animals receiving repeated doses of the product developed antibodies against FVIII that both accelerated its clearance and in some individuals, neutralized its pro-coagulant activity. Therefore, long-term, repeat-dose toxicity studies as well as the standard carcinogenicity bioassay (i.e., 2 years of daily rFVIII dosing in both rats and mice) were not feasible to conduct.

Because rFVIII is a protein, the standard battery of genotoxicity testing as recommended in the International Conference on Harmonization (ICH) S2 guidance documents would not provide information to address potential mutagenicity of the rFVIII and as per the ICH S6 guidance on biotechnology-derived protein therapeutics, these studies were not required. The lack of carcinogenicity, mutagenicity and chronic toxicity data are addressed in the appropriate section of the package insert for NUWIKTM.

No nonclinical reproductive or developmental toxicity studies were conducted in support of this submission. Hemophilia B is an X-linked disorder and affects mostly male subjects; therefore, it is highly unlikely that a pregnant or lactating woman would receive rFVIII. NUWIKTM received labeling that includes a statement in the package insert that nonclinical reproductive and developmental toxicity studies with NUWIKTM have not been conducted, and the product should be used in pregnancy only if clearly needed. This labeling is consistent with that included in prescribing information for other approved recombinant human coagulation factors for the treatment of Hemophilia A or B.

The results from the nonclinical program suggest that the safety profile of NUWIQ™ is sufficient to support its use for the proposed indications of the control and prevention of bleeding episodes, including during and after surgery, in adults and children with Hemophilia A.

Clean Revised Version of Label for Nonclinical

8.1 Pregnancy

Risk summary

There are no data with NUWIQ use in pregnant women to inform on drug-associated risk. Animal Reproduction studies have not been conducted using NUWIQ. It is not known whether NUWIQ can because fetal harm when administered to a pregnant woman or can affect reproduction capacity. NUWIQ should be given to a pregnant woman only if clearly needed. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation

Risk Summary

There is no information regarding the presence of NUWIQ in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NUWIQ and any potential adverse effects on the breastfed infant from NUWIQ or from the underlying maternal condition.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate the carcinogenic potential of Nuwiq or studies to determine the effects of Nuwiq on genotoxicity or fertility have not been performed.

FDA Revisions to Applicant's Label

Applicant's Language (Section edited):

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Animal reproduction studies have not been conducted with FVIII. Based on the rare occurrence of hemophilia A in women, experience regarding the use of FVIII during pregnancy and breast-feeding is not available. Therefore FVIII should be used during pregnancy and lactation only if clearly indicated.

FDA Revision: Section 8.1 was modified to reflect labeling guidelines as per 21 CFR 201.57 Pregnancy and Lactation Label Rule (PLLR) revision.

8.1 Pregnancy

Risk summary

There are no data with NUWIQ use in pregnant women to inform on drug-associated risk. Animal Reproduction studies have not been conducted using NUWIQ. It is not known whether NUWIQ can because fetal harm when administered to a pregnant woman or can affect reproduction capacity. NUWIQ should be given to a pregnant woman only if clearly needed. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Justification: Revised the language to be consistent with that provided in the CFR to describe the Pregnancy Category C designation for NUWIQ to reflect PLLR revises the PLR content and format requirements for subsections 8.1 Pregnancy, 8.2 Lactation, and 8.3 Females and Males of Reproductive Potential of the USE IN SPECIFIC POPULATIONS section of the full prescribing information (FPI) described in 21 CFR 201.56(d)(1) and 201.57(c)(9)(i) through (iii), which removes pregnancy categories and provides descriptive data.

Applicant's Language (Section edited):

8.3 Nursing Mothers

Nuwiq[®] has not been studied in lactating women. It is not known whether this drug is excreted into human milk. Because many drugs are excreted into human milk, caution should be exercised when Nuwiq[®] is administered to a nursing mother. Prescribe Nuwiq[®] only if clinically needed.

FDA Revision: Section 8.3 was modified to reflect labeling guidelines as per 21 CFR 201.57 PLLR revision and relabeled as section 8.2 Lactation in alignment with new PLLR format.

8.2 Lactation

Risk Summary

There is no information regarding the presence of NUWIQ in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NUWIQ and any potential adverse effects on the breastfed infant from NUWIQ or from the underlying maternal condition.

Justification: This section was revised to reflect PLLR revises the PLR content and format requirements for subsections 8.1 through 8.3 of section 8 USE IN SPECIFIC POPULATIONS of the FPI [21 CFR 201.56(d)(1) and 21 CFR 201.57(c)(9)(i) through (c)(9)(iii)], which provides descriptive data for this section.

Applicant's Language (Removed the entire Section 13, below):

13 NON-CLINICAL TOXICOLOGY

Preclinical studies evaluating Nuwiq[®] with rats, dogs, and non-human primates demonstrated efficacy and safety of the product.

FDA Revision: Section 13 removed

FDA Revision: Language immediately related to nonclinical data under the header for Section 13 was removed.

Justification: Removed nonclinical data in Section 13 due to redundancy with the clinical findings. The pharmacodynamic findings in animals are not essential for describing the clinical pharmacology; the Nuwiq product was evaluated for pharmacodynamic activity in clinical trials, and the results and safety profile are appropriately described in the clinical sections of the label.

Applicant's Language (Section edited):

13. Carcinogenesis, Mutagenesis, Impairment of Fertility

Genotoxicity studies and carcinogenicity studies are not applicable for recombinant products. Long-term investigations cannot be performed due to the immune response to heterologous proteins in all non-human mammalian species. Therefore, studies to determine the effects of Nuwiq® on genotoxicity, carcinogenicity or fertility have not been performed.

FDA Revision: Section 13.1

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate the carcinogenic potential of Nuwiq or studies to determine the effects of Nuwiq on genotoxicity or fertility have not been performed.

Justification: Section 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility section was edited to convey important information that was omitted by the Applicant (i.e., an assessment of carcinogenic risk was performed, although in vivo animal carcinogenicity testing was not conducted), and needed to be added to the label.