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

ADDENDUM to the Final Pharmacology/Toxicology Review
Division of Hematology Clinical Review
Office of Blood Research and Review

TO: The file

FROM: Anne M. Pilaro, PhD, Supervisory Toxicologist, Hematology Product Review Branch, Division of Hematology Clinical Review, Office of Blood Research and Review (OBRR), Center for Biologics Evaluation and Research (CBER)

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STN BLA #: 125426/0 (original submission)

APPLICANT: Cangene, Corp., doing business as (DBA) Emergent Biosolutions, Winnipeg, MB, Canada (formerly Inspiration Biopharmaceuticals Inc., Cambridge, MA)

PRODUCT: recombinant, human coagulation Factor IX (IB 1001; IXINITY™) for the control and prevention of bleeding episodes in patients with Hemophilia B, or for the peri-operative management of patients with Hemophilia B

SUBMISSION TYPE: original BLA application

DATE: April 13, 2015

SYNOPSIS:

The purpose of this addendum to the final pharmacology and toxicology reviews for STN BLA #125426/0/0 and STN BLA #125426/0/18 is to provide documentation of the nonclinical sections of the Summary Basis for Regulatory Action (SBRA) and the package insert (i.e., labeling) for the modified-IXINITY™ recombinant, human coagulation Factor IX product. The application for IXINITY™ 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 comment: The final recommendations from the previous nonclinical reviews to approve IXINITY™ for its intended use and patient population have not changed. The nonclinical data submitted in amendment STN BLA#125426/0/18 and in the original BLA submission STN #125426/0/0 support that IXINITY™ is reasonably safe for its intended use in the control and prevention of bleeding episodes, for peri-operative management, and for secondary, tertiary, or intermittent prophylaxis of bleeding episodes in adult and pediatric (12 years of age or older) patients with Hemophilia B. The nonclinical data that supported this decision are described in the respective section of the SBRA, below.

SUMMARY BASIS OF REGULATORY ACTION:

Reviewer comment: The nonclinical studies conducted with former-IXINITY™ were submitted in support of the original BLA submission, and were previously reviewed by Dr. M. Keith Wyatt in his mid-cycle review of the original STN BLA #125426/0 dated September 17, 2012. The "Executive Summary" from Dr. Wyatt's previous memorandum was used as the initial draft for the nonclinical section of the SBRA. The nonclinical pharmacokinetic and immunogenicity bridging data with the modified-IXINITY™ product were submitted as an amendment to the BLA (STN BLA #125426/0/18), and were reviewed by Dr. Anne M. Pilaro in her memorandum dated July 23, 2014. The language for the nonclinical section (i.e., Section 4) of the SBRA has subsequently been modified from Dr. Wyatt's initial draft to include these findings, as well as to address comments received from FDA senior management. The language presented below is what is currently included in the nonclinical section of the SBRA as of the date of this memorandum, and may be subject to further changes prior to the approval of IXINITY™.

"4. Nonclinical Pharmacology/Toxicology

Pharmacological/Toxicological Findings

General Considerations

IXINITY™ was determined to be safe for its intended use as a replacement coagulation factor in patients with congenital FIX deficiency (i.e., Hemophilia B) based on Good Laboratory Practice (GLP) compliant and non-GLP nonclinical studies and on its experimental use during clinical trials. The safety and effectiveness of former-IXINITY™ were characterized in a nonclinical program that included in vivo efficacy testing and induction of thrombogenesis by former-IXINITY™, as well as in vivo pharmacokinetics, local tolerability, and single and repeat-dose toxicity studies in FIX-deficient dogs, and in FIX replete (i.e., wild-type) rats, rabbits, and (b)(4) dogs. A risk assessment of the potential extractable and leachable components present in the IXINITY™ (b)(4) , as per the (b) (4) standards, and nonclinical data to address the comparability of the final commercial modified-IXINITY™ product with the former-IXINITY™ product used in nonclinical and clinical testing were also provided for review.

Previous experience with similar recombinant and plasma-derived FIX products has demonstrated that the toxicities of exogenously administered FIX 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 FIX protein (i.e., immunogenicity), with the potential to cross-react and neutralize endogenous FIX in wild-type animals. The findings with former-IXINITY™, as compared with other marketed FIX products that were included in the testing as part of the IXINITY™ nonclinical program, are discussed in the section below.

During the initial review cycle, 18 of 68 patients receiving former-IXINITY™ in ongoing clinical trials developed measurable titers of antibody directed against host cell proteins (HCP) from the CHO cell line used to produce the drug substance. The CHO HCP contamination was addressed by incorporating an additional (b)(4) step (b)(4) discussed above) in the manufacture of the IXINITY™ drug substance to reduce or remove the HCP, and thereby reduce the immunogenic potential of the drug product. Data from a pharmacokinetic (PK) comparability study in rats designed to evaluate the exposure and kinetics profile of the former- and modified-IXINITY™ products, and from an additional nonclinical study to demonstrate that the immunogenic component(s) had been successfully removed by the manufacturing change were provided, and the results are discussed in the section below.

Nonclinical Findings

Pharmacology

Nonclinical pharmacology studies with former-IXINITY™ were conducted in a canine model of Hemophilia B (i.e., dogs with a naturally occurring mutation/deletion of FIX function), and in normal, FIX-replete (i.e., wild-type) rats. Hemophilic dogs that had been tolerized to human FIX were dosed intravenously with increasing doses of former-IXINITY™, another approved recombinant human FIX product, or a marketed human plasma-derived FIX concentrate in a cross-over study design. Dosing of hemophilic dogs with former-IXINITY™ 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 FIX products. There were no effects of former-IXINITY™ or the other FIX 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-IXINITY™ 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 10-fold greater than the maximum IXINITY™ clinical dose. Biomarker results were similar to those achieved in rats dosed with the comparator groups of an approved recombinant human FIX product, or a marketed human plasma-derived FIX concentrate. No abnormal tissue pathology, and only sporadic evidence of in situ thrombosis with no apparent relationship in the incidence or severity to the FIX dose level were observed on microscopic examination of lung and other tissues from rats dosed with former-IXINITY™ or the comparator FIX products. By contrast, rats dosed with the positive control FEIBA (Factor Eight Inhibitor Bypass Agent) exhibited detectable elevations in ex vivo thrombosis markers, and on microscopic examination showed evidence of thrombi in pulmonary vessels that was dose-related in both incidence and severity.

In summary, animal studies with former-IXINITY™ showed the expected pharmacologic (pro-coagulant) activity in a canine model of Hemophilia B, and the results were similar to those obtained with two other approved human FIX products. There was no evidence of undesirable secondary pharmacologic activity, i.e., thrombogenesis, in FIX-replete rats dosed with former-IXINITY™ or the two approved FIX comparators at dose levels up to10-fold greater than the equivalent human IXINITY™ starting dose. These data were used as proof-of-concept to support the rationale for entering former-IXINITY™ into clinical trials, and to support the pharmacology section of the modified-IXINITY™ BLA Package Insert (PI).

Pharmacokinetics

Pharmacokinetic studies with former-IXINITY™ were conducted concurrently with the pharmacology studies in the human FIX-tolerized, Hemophilia B dogs described above, and FIX activity was measured by both the one-stage clotting (b) (4) . With both assays, the PK profiles from

hemophilic dogs dosed with former-IXINITY™ showed dose-dependent increases in all parameters measured, and were comparable to those obtained when the dogs were dosed with the approved, human recombinant FIX comparator. Similar results were obtained in FIX-replete, wild-type rats with former-IXINITY™ and the two approved, human FIX comparator products. A series of PK studies in FIX-replete, wild-type rats showed that the IXINITY™ products (former and modified) 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 IXINITY™ did not identify any unexpected findings or significant concerns in toxicity studies conducted in wild-type, FIX-replete rats, rabbits, and (b)(4) dogs. (b)(4) dogs dosed with a single, intravenous injection of former-IXINITY™ at doses up to 3-fold greater than the clinical starting dose demonstrated no systemic or tissue pathologies. A repeat dose toxicity study with former-IXINITY™ was conducted only in rats; animals were dosed twice weekly for 28 days by bolus intravenous injection with former-IXINITY™ 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 not consistent or dose-related between the former-IXINITY™ dose groups, and no corresponding histopathological findings were detected. The findings in the former-IXINITY™ dosed rats were comparable to those receiving an equivalent dose of either an approved, recombinant human FIX product or a human plasma-derived FIX concentrate as comparators, suggesting that the safety profile of former-IXINITY™ is similar to that of other, approved FIX products. Dermal toxicity and local tolerance studies conducted in rabbits administered the clinical dose of former-IXINITY™ revealed acceptable levels of inflammation and edema at the injection site.

There were no animal studies for carcinogenicity, in vitro or in vivo mutagenicity, fertility, reproductive toxicity or teratogenicity conducted with IXINITY™. IXINITY™ is a recombinant, human protein and animals receiving repeated doses of the product developed antibodies against FIX that both accelerated clearance of the protein and in some cases, 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 IXINITY™ dosing in both rats and mice) were not feasible to conduct.

Because IXINITY™ is a protein, the standard battery of genotoxicity testing as recommended in the International Conference on Harmonisation (ICH) S2 guidance documents would not provide information to address potential mutagenicity of the rFIX, 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.

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 IXINITY™. IXINITY™ received a Pregnancy Category C designation in the labeling that includes a statement that nonclinical reproductive and developmental toxicity studies with IXINITY™ have not been conducted, and the product should be used 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.

Special Toxicology Studies

A repeat-dose study in (b)(4) rabbits was conducted to compare the immunogenicity of residual CHO host cell proteins in the IXINITY™ drug product manufactured by the modified commercial manufacturing process (modified-IXINITY™) with the former-IXINITY™ used in the

clinical trials. No remarkable toxicities were reported in rabbits after intravenous dosing twice weekly for 18 doses (9.5 weeks) with either former- or modified-IXINITY™. However, the modified manufacturing process for IXINITY™ resulted in a decrease in the immunogenicity of the final drug product. At the end of the treatment period, there was a marked, statistically significant decrease in the incidence of immunogenicity to the CHO host cell proteins in rabbits dosed with modified-IXINITY™, compared to animals injected with former-IXINITY™. Comparable exposures to human rFIX, as measured by the Area Under the Concentration versus Time Curve were demonstrated in a PK study in rats, after a single intravenous injection of either the former- or modified-IXINITY™ products. Taken together, these nonclinical data can be used to successfully bridge the nonclinical safety profile of the former- and modified-IXINITY™ drug products, establish that the modified-IXINITY™ drug product results in decreased immunogenicity in animals with comparable drug exposure to the former-IXINITY™ product and suggest that modified-IXINITY™ significantly reduced potential for anti-CHO host cell protein antibody development in patients with Hemophilia B receiving the product for the proposed indications, with a resulting improvement in product safety.

Toxicologic risk assessment analysis

A toxicological risk assessment analysis, providing identification and qualification of the safety of the extractable and potential leachable substances from the components used in the IXINITY™ manufacturing process, was also provided. The results of this risk analysis indicated that the levels of potential leachable or extractable impurities appear acceptable, as they were significantly lower than the maximally allowed daily exposure levels identified from extensive clinical and nonclinical experience. Additionally, the safety of these extractable and leachable compounds can be considered adequately qualified because several lots of IXINITY™ were used in the nonclinical toxicology testing, at daily doses of rFIX exceeding the recommended clinical dose by up to 10- to 14-fold. The risk of the presence of these compounds to patients with Hemophilia B receiving intravenous doses of IXINITY™ for treatment or perioperative management of bleeding at the levels identified is considered minimal, and acceptable considering the benefit of FIX replacement therapy in this population.

Recommendation

The results from the nonclinical program suggest that the safety profile of modified-IXINITY™ is sufficient to support its use for the proposed indications of on-demand treatment and the perioperative management of children ≥12 years of age and adult patients with Hemophilia B."

LABELING REVIEW:

The draft labeling provided by Cangene was revised to reflect the current labeling guidelines, and to include relevant information for prescribing, based on the nonclinical and clinical experience using IXINITY™ that was provided in the BLA. The initial language in the package insert (as provided by Cangene), the FDA revisions and their justification are documented in this memorandum, below.

Reviewer comment: Draft labeling was not reviewed by Dr. Wyatt in his mid-cycle or his final pharmacology and toxicology reviews for STN BLA #125426/0. The relevant nonclinical sections of the labeling (**HIGHLIGHTS** – USE IN SPECIFIC POPULATIONS; **Section 8.1**, Use in Pregnancy; **Section 8.3**, Nursing Mothers, and **Section 13.1** Carcinogenesis, Mutagenesis, Impairment of Fertility) were reviewed and revised by Dr. Pilaro on January 8, 2015 directly in the shared document, and are presented below.

HIGHLIGHTS – USE IN SPECIFIC POPULATIONS
Applicant's language:

- "Pregnancy: There is no human or animal data available. IXINITY should be used during pregnancy and lactation only if clearly indicated (8.1).
- Nursing Mothers: Use only if clearly indicated (8.2)."

FDA revisions:

- *Pregnancy: No human or animal data are available. Use IXINITY during pregnancy only if clearly needed (8.1).*
- *Nursing Mothers: Use IXINITY only if clearly needed (8.3).*

Justification: Revised the language to be consistent with that provided in the 21 CFR 201.57, and Sections 8.1 (Use in Pregnancy) and 8.3 (Nursing Mothers) of the Full Prescribing Information.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Applicant's language:

"Pregnancy Category C

Animal reproduction studies have not been conducted with IXINITY. Based on the rare occurrence of hemophilia B in women, experience regarding the use of factor IX, including IXINITY during pregnancy and breast-feeding, is not available. It is not known whether IXINITY can affect reproductive capacity or cause fetal harm when given to women. Therefore, IXINITY should be used during pregnancy and lactation only if clearly indicated."

FDA revisions:

Pregnancy Category C

Animal reproduction studies have not been conducted with IXINITY. It is also not known whether IXINITY can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. IXINITY should be given to a pregnant woman only if clearly needed.

Justification: Revised the language to be consistent with that provided in the 21 CFR 201.57 to describe the Pregnancy Category C designation for IXINITY™.

8.3 Nursing Mothers

Applicant's language:

"8.2 Nursing Mothers/Lactation

It is not known whether IXINITY is excreted into human milk. Because many drugs are excreted into human milk, caution should be exercised if IXINITY is administered to nursing mothers."

FDA revisions:

8.3 Nursing Mothers

It is not known whether IXINITY is excreted into human milk. Because many drugs are excreted into human milk, caution should be exercised when IXINITY is administered to a nursing woman.

Justification: Revised the language to be consistent with that provided in the 21 CFR 201.57 and the FDA guidance on the Physician's Labeling Rule to describe the risk of IXINITY™ in nursing mothers.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Applicant's language:

"No investigations on genotoxicity, carcinogenicity, or toxicity to reproduction, and development have been conducted.

No adverse effects on reproductive organs were observed by macroscopic and microscopic pathological investigations in repeated dose toxicity studies. No investigations on impairment of fertility have been conducted."

FDA revisions:

No nonclinical investigations of genotoxicity, carcinogenicity, or toxicity to reproduction and development have been conducted with IXINITY.

No macroscopic or microscopic pathologies in reproductive organs were observed in repeated dose toxicity studies of IXINITY in animals. No animal studies regarding impairment of fertility following IXINITY dosing were conducted.

Justification: Revised the language to reflect the actual data provided in the BLA.