



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 Primary Discipline Review
Division of Hematology
Office of Blood Research & Review

To: The file (Original BLA STN 125506/0)

From: Yolanda Branch, PhD, Pharmacologist, Division of Hematology Clinical Review (DHCR)/Office of Blood Research and Review (OBRR)

Through : Anne M. Pilaro, PhD, Supervisory Toxicologist, DHCR/OBRR/CBER

BLA#: STN 125506/0

Applicant: Bio Products Laboratory Limited (BPL)

Product: Plasma-derived Coagulation Factor X (COAGADEX)

Subject: Addendum to the final Pharmacology/Toxicology Discipline review for human plasma-derived Factor X, for the treatment of hereditary Factor X deficiency

Overview

The purpose of this addendum to the final pharmacology and toxicology review for STN BLA #125506/0 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 human plasma-derived coagulation Factor X. The application for COAGADEX 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 COAGADEX for its intended use and patient population have not changed. The nonclinical data submitted in the original BLA submission STN #125506/0 support that COAGADEX is reasonably safe for its intended use in the treatment of bleeding episodes, and to control bleeding during surgical procedures in patients with hereditary Factor X deficiency. The nonclinical data that supported this decision are described in the respective section of the SBRA, below.

Summary Basis for Approval (SBRA)

Nonclinical Pharmacology/Toxicology

Pharmacology Studies

The primary pharmacodynamics activity of Factor X was demonstrated using *in vitro* studies. Addition of COAGADEX to Factor X deficient rat plasma corrected or restored the prolonged activated partial thromboplastin time (aPTT) and prothrombin times (PT) to levels within the range of normal plasma, in a dose-dependent manner. These results were similar to those obtained with another approved comparator Factor IX P Behring. When tested using an *in vivo* thrombus generation assay (i.e., the (b) (4) assay in rabbits), there was no statistical difference in thrombus formation between the groups of rabbits dosed with either normal plasma or normal plasma containing COAGADEX. Nonclinical *in vivo* studies of primary pharmacodynamics were not performed in animals due the lack of an available animal model for Factor X deficiency.

In summary, the nonclinical pharmacodynamic studies with COAGADEX showed the pro-coagulant activity in an *in vitro* model of Factor X deficiency, and the results were similar to those obtained with another approved PCC concentrate. There was no increase in thrombogenicity in rabbits dosed with COAGADEX plus normal plasma, when compared to those rabbits dosed with normal plasma alone. These data were used as proof-of-concept to support the rationale for entering COAGADEX into clinical trials.

Pharmacokinetic Studies

The initial pharmacokinetic FX profile was obtained in COAGADEX-dosed (b) (4) rats. Factor X activity was measured using a chromogenic substrate assay. The pharmacokinetic profile in (b) (4) rats showed a dose-dependent increase in all parameters measured, with linear, dose-proportional increases in both the maximum plasma concentration (C_{max}) and exposure (area under the concentration-time curve, AUC) with increasing doses of COAGADEX.

Toxicology

Overall, toxicity studies with COAGADEX conducted in (b) (4) rats and did not identify any unexpected findings or significant concerns. (b) (4) rats dosed with a single intravenous injection of COAGADEX at doses up to 24-fold greater than the maximum clinical dose demonstrated no systemic or tissue pathologies. In a 28-day, repeat dose toxicity study with COAGADEX in rats, animals were dosed every other day by bolus intravenous injection with COAGADEX doses equal to, and up to 14-fold greater than, the clinical starting dose. Although statistically significant differences in some measured parameters were reported, the findings were not consistent or dose-related between the COAGADEX dose groups, and no corresponding histopathological findings were detected. Animal findings for toxicity studies were expected, and consistent with the exaggerated pharmacologic effects reported with other recombinant and plasma-derived coagulation factors. Local tolerance study conducted in rabbits administered the clinical dose of COAGADEX 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 plasma-derived Factor X. As Factor X is a plasma-derived human protein,

animals receiving repeated doses of the product developed antibodies against Factor X. Therefore, long-term, repeat-dose toxicity studies, as well as the standard carcinogenicity bioassay (i.e., 2 years of daily Factor X dosing in both rats and mice) were not feasible to conduct.

Because Factor X is a protein, the standard genotoxicity testing recommended in the ICH S2 guidance documents would not provide information to address potential mutagenicity of Factor X, 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 COAGADEX.

No nonclinical reproductive or developmental toxicity studies were conducted. COAGADEX labeling includes a statement that nonclinical reproductive and developmental toxicity studies have not been conducted, and COAGADEX should be used during pregnancy or lactation only if clearly needed. This labeling is consistent with that included in prescribing information for other approved recombinant and plasma-derived human coagulation factors.

Nonclinical Label for Package Insert (PI) for BLA 125506/0

The label was revised to reflect current labeling guidelines and the relevant information for prescribing data based on nonclinical and clinical experience using COAGADEX.

LABELING REVIEW

The draft labeling provided by BPL was revised to reflect the current labeling requirements under the 2014 Pregnancy and Lactation Labeling Rule, and to include relevant information for prescribing, based on the nonclinical and clinical experience using COAGADEX that was provided in the BLA. The initial language in the package insert (as provided by BPL), 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 #125506/0. 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) are revised and are presented below.

Labeling Revisions to Applicant's Label **Clean Revised Version of Label for Nonclinical**

8.1 Pregnancy

Risk summary

There are no data with COAGADEX use in pregnant women to inform on drug-associated risk. Animal reproduction studies have not been conducted using COAGADEX. It is not known whether COAGADEX can because fetal harm when administered to a pregnant woman or can affect reproduction capacity. COAGADEX 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 COAGADEX 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 COAGADEX and any potential adverse effects on the breastfed infant from COAGADEX or from the underlying maternal condition.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Nonclinical studies evaluating the carcinogenic potential of COAGADEX have not been conducted. A bacterial reverse mutation test (b) (4)) and a chromosome aberration test in human lymphocytes demonstrated no evidence of mutagenic activity using COAGADEX

FDA Revisions to Applicant's Label

8 PREGNANCY AND LACTATION

Applicant's Language:

8.1 Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with Replafacten. It is not known whether Replafacten can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Replafacten should be administered to pregnant women only if clinically needed.

FDA Revision: Section 8.1 was modified to reflect labeling guidelines as per the 2014 Pregnancy and Lactation Labeling Rule.

8.1 Pregnancy

There are no data with COAGADEXTM use in pregnant women to inform on drug-associated risk. Animal reproduction studies have not been conducted using COAGADEXTM. It is not known whether COAGADEXTM can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. COAGADEXTM 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 Nursing Mothers

It is not known whether COAGADEX is excreted in human milk. Because many drugs are excreted in human milk, use COAGADEX only if clearly needed when treating a nursing woman.

FDA Revision: Section 8.1 was modified to reflect labeling guidelines as per the 2014 Pregnancy and Lactation Labeling Rule.

13 NONCLINICAL TOXICOLOGY

Applicant's Language:

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Human plasma coagulation factor X (as contained in REPLAFACTMTEN) is a normal constituent of the human plasma and acts in the same way as the endogenous factor X.

Single dose toxicity studies in rats established a no-observed-effect-level of >2400 IU/kg body weight, a greater than 40 fold safety margin. Repeat dose toxicity studies in rats, with repeated administration every 2 days, established a no-observed-effect level at 30 IU/kg body weight. The no-observed-adverse-effect-level was above the highest dose in the study (360 IU/kg body weight), a greater than 6 fold safety margin.

Thrombogenicity testing in rabbits showed that the thrombogenicity of REPLAFACTMTEN at doses of 100-400 IU/kg body weight was not significantly different to that of the physiological saline negative control.

Local tolerance studies established that REPLAFACTMTEN had good tolerability when administered by the intravenous route at a dose of 600 IU/kg body weight (10 fold safety margin). A slightly less but still fully acceptable tolerability was found following paravenous injections at 211-370 IU/kg body weight (3.5-6.2 fold safety margin). Visible local erythema, oedema and tissue inflammation were present when administered by intra-arterial, or inadvertently by peri-arterial, injections at a dose of 600 IU/kg body weight (10 fold safety margin). These were tolerable with no evidence of ongoing damage. Visible local signs had resolved by day 8.

FDA Revision: Revised the language to reflect the actual data provided in the BLA, and to change the proprietary name to the current, FDA permitted name.

Nonclinical studies evaluating the carcinogenic potential of COAGADEX have not been conducted. No macroscopic and microscopic pathologies in reproductive organs were observed in repeated dose toxicity studies of COAGADEX in animals. No animal studies regarding impairment of fertility following COAGADEX dosing were conducted.