MEMORANDUM

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FDA / CBER / OTAT / DCEPT

BLA 125612/0	
Submission date	June 9, 2016
Review date	June 1, 2017
Product Reviewers	Ze Peng, PhD (OTAT) Randa Melhem, PhD (OCBQ)
Pharm / Tox Reviewer	Ying Huang, PhD (OTAT)
Clinical Reviewers (clinical studies, Pharmacovigilance, BiMO)	Bindu George, MD (OTAT) Victor Baum, MD (OBRR) Faith Barash, MD, MPH (OBE) Anthony Hawkins, MS (OCBQ) Colonious King (OCBQ)
Clinical Pharmacology Reviewer	Iftekhar Mahmood, PhD (OTAT)
Statistical Reviewer	Shuya Lu, PhD (OBE)
Device Reviewer	Sapana Patel, PharmD (CDRH) Rakhi Dalal, PhD (CDRH)
Regulatory Project Manager	Thomas Maruna
Applicant	Octapharma Pharmazeutika Produktionsges.m.b.H.
Product/Trade Name	Fibrinogen (Human)/FIBRYNA
Proposed Indication	For the treatment of acute bleeding episodes in adults and adolescents with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia. Fibryna is not indicated for dysfinbrinogenemia.
Recommendation	Approval

Executive Summary

Octapharma submitted this Biologics License Application (BLA) to seek U.S. licensure for human fibrinogen (FIBRYNA) for the treatment of acute bleeding episodes in adults and adolescents with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia. FIBRYNA is not indicated for dysfibrinogenemia.

Please see primary reviews from Drs. Victor Baum and Bindu George (clinical), Dr. Shuya Lu (statistical), Dr. Ying Huang (pharmacology/toxicology), and Dr. Faith Barash (pharmacovigilance) for detailed reviews of this original BLA. The review team recommends approval of this BLA for the above indication.

I concur with the review team's recommendation on approval of the BLA for the treatment of acute bleeding episodes in adults and adolescents with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia.

Notable Review Issues

Octapharma provided the results of two clinical studies (FORMA 01 and FORMA 02) in support of the safety and efficacy of FIBRYNA for the treatment of both acute minor and major bleeding episodes as well as perioperative management of bleeding in patients with congenital fibrinogen deficiency. Although, there are limited efficacy and safety data for doses required to treat major bleeding (target fibrinogen levels of 150 mg/dL), there is sufficient data from the clinical studies to support approval of FIBRYNA for major bleeding as successful hemostasis was documented in a limited number of subjects who achieved target fibrinogen levels of > 140 mg/dL. Additionally, the published data supports control of bleeding at lower plasma fibrinogen levels of 100mg/dL. (b) (4)

Although no significant safety signals were identified with FIBRYNA based on the data from FORMA 01 and FORMA 02, a paradoxical risk of thrombosis has been documented in the published literature with fibrinogen replacement therapy. As there is very limited data in subjects dosed to target fibrinogen levels of 150 mg/ dL, the dose recommended for major bleeding and more likely to be associated with thromboembolic events, a post-marketing study will be required as a PMR to evaluate the risks of thromboembolic events in adults and adolescent subjects in the treatment of major bleeding.

Recommendations

Approval is recommended for the treatment of minor and major bleeding episodes in adults and adolescents with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia as the clinical evidence provided in this BLA supports the safety/effectiveness of FIBRYNA for these indications. However, a post-marketing study to assess the risk of thromboembolic events with the use of FIBRYNA in the treatment of major bleeding episodes will be required.