SUMMARY REVIEW OF DIVISION DIRECTOR

Application Number	**BLA 125294 S-045**
Application Type	351(a)
Priority or Standard	Standard
Submit Date	1/31/2018
Received Date	1/31/2018
PDUFA Goal Date	7/20/2018
Division/Office	DHP/OHOP
Review Completion Date	7/23/2018
Applicant	Sicor Biotech
Established Name	Tbo-filgrastim
Trade Name	Granix
Pharmacologic Class	Filgrastim Growth Factor
Formulations	300 mcg/0.5ml and 480 mcg/0.8ml in single-dose prefilled syringe
Dosing Regimen	5 microgram/kg sc daily
Proposed Indication/Population	In adult and pediatric patients 1 month and older for reduction in the duration of severe neutropenia in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia
Recommended Regulatory Action	Approval

Resources consulted:

DHP Reviewers	Lea Cunningham, MD, PhD and Donna Przepiorka, MD, PhD
Biostatistics	Yaping Wang, PhD and Yuan Li Shen, PhD

Division Director's Summary Review of BLA 125294 S-045

(This review was based in part on the reviews of Dr. Donna Przepiorka, Dr. Yaping Wang, and Dr. Lea Cunningham.)

Background: On December 8, 2017, Sicor Biotech UAB submitted NDA 125294 S-045 in which the Sponsor requested that PMR 2333-1, which appeared in the original approval letter for tbo-filgrastim (Granix) for NDA 125294 dated August 29, 2012, be classified as fulfilled. The following wording in PMR 2333-1 appeared in the original approval letter: "Phase 2 trial in 50 pediatric patients 1 month to 16 years of age to evaluate pharmacokinetics, pharmacodynamics, and safety data in patients with solid tumors without bone marrow involvement. Submit the protocol for Agency review and concurrence prior to beginning the trial and in advance of the "final protocol submission" date so that agreement on the essential trial elements can be reached." The date by which the final report was to be submitted was originally December 20, 2016, but this was changed eventually to March 20, 2018.

The request of Sicor Biotech for designation of PMR 2333-1 as being fulfilled relied upon Study XM02-ONC-201 which was a single arm multicenter, open-label study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, efficacy and immunogenicity of daily subcutaneous administration of 5 µg/kg of tbo-filgrastim in infants, children and adolescents with solid tumors without bone marrow involvement. Study XM02-ONC-201 was also the subject of a written request. The treatment consisted of the administration of myelotoxic chemotherapy which is known to be sufficiently intensive such that it induces a neutrophil nadir of less than 0.5 X 10^9/L. Next, 24 hours after the last chemotherapy, daily subcutaneous administration of 5 µg/kg of tbo-filgrastim was carried out. The treatment with tbo-filgrastim continued daily for as long as required to pass the neutrophil nadir and the time at which the neutrophil count had recovered to 2.0 X 10^9/L but not longer than 14 consecutive days.

The primary endpoint was safety in all patients in the intent to treat population who received at least 1 dose of tbo-filgrastim and had at least 1 post baseline efficacy assessment (50 patients). Secondary endpoints included pharmacokinetic measurements (serum concentration of tbo-filgrastim) and pharmacodynamic measurements (the absolute neutrophil count (ANC)) in the peripheral blood from which the incidence and duration of severe neutropenia (defined as any ANC value <0.5 X 10^9/L at any time) and the incidence of febrile neutropenia were derived.

Efficacy Results: In the 1 month to <2years age group, 2 patients were enrolled. In the 2 to <12 years age group, there were 30 patients enrolled. In the 12 to <16 years age group, there were 18 patients enrolled. The pharmacokinetic parameter values for Cmax and AUC0-12 overlapped in all age groups. The median (range) tmax was 4.05 hours (3.9 to 8.0) and there were no apparent differences amongst the different age groups for which the ranges overlapped.

The incidence of severe neutropenia for all age groups was 52% (26/50) [95% CI: 0.374, 0.663]. It was 63% (19/30) in the 2 to <12 years age group [95%CI: 0.439, 0.801] and 33% (6/18) in the 12 to <16 years age group [95% CI: 0.133, 0.590]. One of the 2 infants in the 1 month to <2 years age group experienced severe neutropenia.

The time to the ANC nadir from the beginning of tbo-filgrastim administration was a mean of 6.9 days for the 2 to <12 years age group and 7.3 days in the 12 to <16 years age group. The mean time to ANC recovery to ≥1.0 X 10^9/L from the tbo-filgrastim administration was 7.3 days in the 2 to <12 years versus 5.1 days in the 12 to <16 years age group.

No clinically relevant differences were observed in the pharmacokinetics of tbo-filgrastim given at 5 µg/kg/day in 49 pediatric patients (1.4 to 15.9 years) after chemotherapy. The incidence of febrile neutropenia overall was 26% (13/50): 30% (9/30) in the 2 to <12 years age group and 17% (3/18) in the 12 to <16 years age group.

Safety Results: There were no TEAE leading to death, discontinuation, or withdrawal from the study**.** Serious TEAEs were reported in 24% (12/50) overall. Treatment emergent adverse events considered to be treatment related were reported in 18% (9/50) overall: 13% in the 2 to <12 years age group and 28% of patients in the 12 to <16 years age group. The most frequently occurring TEAEs were in the following SOCs: blood and lymphatic system (72%), gastrointestinal disorders (40%), general disorders and administration site conditions (24%), investigations (16%), metabolism and nutrition disorders and skin and subcutaneous tissue disorders (12% each), infections and infestations (14%) and musculoskeletal and connective tissue disorders (10%). There were no allergic reactions or unexpected safety findings. The pharmacokinetics and safety profile of tbo-filgrastim in the pediatric population were similar to those seen in adults.

Benefit Risk Discussion The efficacy data indicate that tbo-filgrastim is effective in children and adolescents, and the safety data indicate that tbo-filgrastim was well tolerated in children and adolescents. The benefit risk profile is favorable**.**

Recommended Regulatory Action: This Supervisory Associate Division Director reviewer agrees with the recommendation of the review teams that the BLA 125294 S-045 be approved and that the PMR 2333-1 and the written request be considered fulfilled. In addition, I recommend that the label be updated to state in Section 8.4 that the safety and effectiveness of Granix have been established for pediatric patients 1 month to <17 years old and that the indication be changed to include pediatric patients 1 month and older.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ALBERT B DEISSEROTH
07/23/2018