CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125294Orig1s000

OFFICE DIRECTOR MEMO

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Richard Pazdur, MD
Subject	Office Director Summary Review
NDA/BLA # **Supplement #**	125294
Applicant Name	Sicor Biotech UAB
Date of Submission	Original BLA 11/30/09; Resubmission 2/29/12
PDUFA Goal Date	8/29/12
Proprietary Name / **Established Name**	No proprietary name/tbo-filgrastim
Dosage Forms / Strength	Solution for subcutaneous injection in pre-filled syringes with and without needle guard 300mcg/0.5 mL and 480mcg/0.8mL
Proposed Indication(s)	To reduce the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package for this cycle, including:	
Division Director	Ann Farrell, MD
Medical Officer Review	Thomas Herndon, MD/Albert Deisseroth, MD, PhD
Statistical Review	Qing Xu, PhD/Mark Rothmann, PhD
Pharmacology Toxicology Review	Robeena Aziz, PhD/Haleh Saber, PhD/John Leighton, PhD
CMC Review/OBP Review	Jee Chung, PhD/Dov Pluznik, PhD/Kathy Lee, MS/Emanuela Lacan, PhD
Microbiology Review	Kalavati Suvarna, PhD/Patricia Hughes Troost, PhD
Clinical Pharmacology Review	Joseph Grillo, PhD/Julie Bullock, PharmD/Nam Atiqur Rahman, PhD
DDMAC	James Dvorsky
DSI	Lauren Iacono-Connors, PhD/Susan Liebenhaut, MD/Tejashari Purohit Sheth, MD
CDTL Reviews	Albert Deisseroth, MD, PhD
Other – Pediatric and Maternal Health Team Other- Pharmacometrics	Jeanine Best, RNP/Hari C. Sachs, MD/Lisa Mathis, MD

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology

1. Introduction

On November 30, 2009, Teva submitted a biologics licensing application (BLA) under section 351(a) of the Public Health Service (PHS) Act for tbo-filgrastim (Sponsor's name of compound is XM-02), and the Agency issued a Complete Response letter for this application on September 29, 2010. See Dr. Farrell's Division Director Summary Review for the contents of the Complete Response letter issued by the Agency in September 2010. On February 29, 2012, the Sponsor submitted a Class 2 resubmission addressing all of the deficiencies in the Agency's September 29, 2010, Complete Response letter.

Tbo-filgrastim is a biological protein. Tbo-filgrastim can be referred to as a granulocyte colony stimulating factor (G-CSF). The applicant has proposed the following indication: to reduce the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

In 2008, Teva obtained market authorization in the EU under an EMA abbreviated pathway for biosimilar products. In the US, Teva submitted its application under section 351(a) of the PHS Act. Many aspects of Teva's previously completed development program were not relevant to a submission under section 351(a) of the PHS Act. However, with the submission of additional data, this application contains all necessary nonclinical, clinical pharmacology, and clinical trial data necessary to support licensure of tbo-filgrastim for the single indication proposed by Teva. The applicant does not rely on any proprietary data submitted to another BLA to support the safety and efficacy of tbo-filgrastim.

The original submission contained one pivotal clinical trial comparing tbo-filgrastim to a non-US-approved filgrastim and to placebo. The key efficacy comparison for this application, and that upon which the demonstration of effectiveness relies, is the comparison of tbo-filgrastim to placebo.

On April 5, 2012, Teva Pharmaceuticals notified the Agency of a change in sponsorship of this BLA from Teva Pharmaceuticals to Sicor Biotech UAB.

2. CMC/Device

The Office of Biotechnology Products (OBP) has not identified any issues that would preclude approval. The reviews noted that the product is well-characterized and that the manufacturing processes are well-controlled and consistent. Facilities inspections (substance) performed during the first cycle also did not uncover any issues that have precluded approval and there are no current issues involving the drug substance or drug product manufacture that would preclude approval.

OBP agreed with the applicant's request for a categorical exclusion. The OBP review states that the drug substance (b) (4) (b) (4) are stable when stored at (b) (4) for up to (b) (4) and the drug product is stable when stored at 2-8°C for up to 36 months.

CMC/OBP has asked Teva to perform additional testing for immunogenicity issues related to their antibody assay. CMC/OBP state in their review that the additional testing is not an approvability issue because immunogenicity-related issues such as extended neutropenia or loss of efficacy were not observed in the clinical trials. The requested additional testing will be part of the post marketing requirements.

(b) (4)

. The applicant addressed other issues regarding how the pre-filled syringe (device) performs. These issues are considered by CDRH to have been adequately addressed.

3. Nonclinical Pharmacology/Toxicology

The nonclinical safety of tbo-filgrastim was assessed in two GLP 26-week repeat dose toxicity studies with a 4 week recovery period in rats and monkeys. GLP safety pharmacology studies were also performed. Major toxicities identified were bone marrow hypercellularity, extramedullary hematopoiesis, increased alkaline phosphatase, painful joints (paws and limbs), and granulocyte infiltration. No effects were observed on the respiratory, cardiovascular or central nervous system.

Genotoxicity and carcinogenicity studies were not performed as these studies are not appropriate for large molecular weight proteins and the carcinogenicity study would not be necessary based on the indicated population.

During the first review cycle, there was only 1 issue identified which precluded approval: lack of an assessment of developmental and reproductive toxicity of XM02 in at least one relevant animal species. The relevant animal species identified and recommended was the rabbit.

The applicant submitted a nonclinical study satisfactorily addressing this issue. The following text is from the pharmacology/toxicology team leader's review:

The current submission contains results of an embryofetal developmental toxicology study in rabbits, conducted with XM02. This study adequately addresses the nonclinical deficiency identified in 2010.

In brief, pregnant rabbits were treated with XM02 during the period of organogenesis. The adverse embryofetal effects are consistent with those reported for approved products (e.g. Neupogen) and those reported in published articles for other G-CSF products. Findings in rabbits include: spontaneous abortion, increased post-implantation loss, reduced fetal weight, reduced litter size, and malformations. Adverse findings are most evident at the high dose of 100 µg/kg/day. This dose resulted in significant increases in white blood cells (WBCs) and differentials.

There are no issues that preclude approval.

4. Clinical Pharmacology/Biopharmaceutics

The original review of this application did not identify any deficiencies which would preclude approval. The original package contained pharmacokinetic and bioavailability studies in healthy volunteers and tbo-filgrastim's pharmacokinetics were assessed in subgroups of patients with cancer.

The following text is from Dr. Keegan's summary review of this application:

The median T_{max} was 6 hours and the median half-life ($t_{½}$) was 8.9 hours for the 5 mcg/kg dose in healthy volunteers. Increasing the dose of XM02 from 5 to 10 mcg/kg resulted in an approximately 3-fold increase in both C_{max} and AUC 0-48h. In patients with cancer receiving chemotherapy, the median T_{max} of XM02 ranged from 4 to 6 hours and the median $t_{½}$ ranged from 3.2 to 3.8 hours. Accumulation after repeated daily dosing was not observed. Based on this cross-study comparison, the pharmacology reviewer concluded that there were no interactions regarding dose adjustment based on the underlying cancer or chemotherapy regimen, across the limited numbers of cancer and chemotherapy regimens included in these studies.

No gender-related differences were observed in the pharmacokinetics of XM02 administered by the subcutaneous route of administration. Mild renal impairment (creatinine clearance 60–89 mL/min; N=11) had no clinical meaningful effect on XM02 pharmacokinetics. No dose adjustment is recommended for mild renal impairment. The pharmacokinetic profile in patients with moderate and severe renal impairment has not been assessed. However, based on the safety margin of XM02 and the lack of relationship between the incidence of the major adverse event (bone pain) and degree of renal impairment, an XM02 dosage adjustment would not be clinically warranted. The pharmacokinetic profile in patients with hepatic impairment has not been studied.

The review team recommended approval with a PMR for the QT study. The September 2010 Complete Response letter recommended that the applicant conduct a Thorough QT (TQT) study.

The applicant submitted a protocol for a TQT study, which the IRT review team reviewed with comments to be sent to the applicant. The lack of a completed TQT study does not preclude approval and will be addressed as a PMR.

5. Clinical Microbiology

During the first cycle review, product quality microbiology issues were identified that would preclude approval. The text below is from the review:

Due to several proposed changes to the filgrastim drug substance manufacturing process to improve microbial control, please submit the following data as soon as they are available:

a. In-process and final filgrastim bioburden and endotoxin data for the (b) (4) following the proposed changes.
b. Microbial control data for storage (b) (4)
c. Any other changes and data that could affect microbial process control (for example, changes in hold times).

The applicant responded to these deficiencies within this submission. The microbiology team reviewed the submission and recommended approval. The review team also recommended three postmarketing commitments (PMCs). Please refer to the action letter for these PMCs.

There are no outstanding clinical microbiology or sterility issues that preclude approval.

6. Clinical/Statistical-Efficacy

One pivotal trial was submitted for this indication. However, several additional trials were submitted which provided additional supportive safety data. There were two phase 1 trials in healthy volunteers and three phase 3 trials. The trial enrolling patients with breast cancer was pivotal for the indication. The other phase 3 trials in lung cancer and non-Hodgkin's Lymphoma were important for safety assessment.

XM02-02 was a large, international, multicenter, randomized controlled trial randomizing 350 patients with breast cancer (Stage II to IV) receiving initial chemotherapy to XM02, a non-US-approved filgrastim product, and placebo treatment. The primary efficacy endpoint was the duration of severe neutropenia. The trial had two planned comparisons: XM02 arm with placebo and XM02 with non-US-approved filgrastim product. The results after adjustment for "treatment", "country" and "adjuvant vs. metastatic therapy" and baseline absolute neutrophil count revealed a statistically significant difference ($P< 0.0001$, X^2) in mean duration of severe neutropenia in cycle 1 between the XM02 arm (mean duration 1.1 days) and placebo arm (mean duration, 3.8 days).

The statistical review team performed several sensitivity analyses due to applicant's method of data imputation for missing data to ensure the robustness of the applicant's result for the primary comparison.

The utility of the comparison to the non-US-approved filgrastim product is uncertain. The applicant's proposal for an equivalence or non-inferiority comparison was not discussed and agreed upon with the Agency prior to submission. A non-US-approved filgrastim product and US-licensed Neupogen are considered two separate products. No data has been submitted to compare them. The applicant did not provide justification for the one day margin. Therefore the comparison to the non-US-approved filgrastim product is not considered relevant for regulatory purposes to demonstrate the safety, potency, and purity of tbo-filgrastim. As noted above, the demonstration of effectiveness was based only on the data generated by the comparison of tbo-filgrastim to placebo.

7. Safety

The safety database was adequate. Approximately 750 patients and healthy volunteers received at least one dose of tbo-filgrastim. Approximately 680 patients were enrolled in the phase 3 trials. Of those 680 patients, 541 patients received tbo-filgrastim. The primary safety review concentrated on the 541 patients in the three clinical trials who received tbo-filgrastim.

During the first cycle review, Dr. Herndon reviewed all available sources of safety data and noted that one patient had an allergic reaction (after the tenth dose of XM02) and that bone pain was observed in 24% of patients receiving XM02 and 31% of patients receiving the non-US-approved filgrastim. The difficulty with adverse event attribution in the pivotal trial was the fact that patients were receiving chemotherapy as well therefore many of the serious adverse events noted were due to chemotherapy and not XM02.

Immunogenicity
During the first cycle, the review teams determined that the immunogenicity testing using assays that were not validated was not considered reliable. However, these assays suggested that no patients enrolled in XM02-02 had binding antibodies or neutralizing antibodies during treatment. Review of the trial database did not reveal any patients treated with XM02 who had an unusually prolonged period of neutropenia which would suggest the development of antibodies. Therefore the review teams (clinical and OBP) decided that further study of the immunogenicity issue could be performed post-approval as a post-marketing requirement.

The review team for the current and original submissions did not recommend a REMS.

8. Advisory Committee Meeting

Since this is the fourth application for a product for the prevention of severe neutropenia and no unexpected clinical efficacy or safety issues were observed, no advisory committee meeting was held.

9. Pediatrics

During the first review cycle, the application had a requested a partial waiver based on age (less than 1 month of age) and a deferral of pediatric studies as a post-marketing requirement. Both were granted. The deferred pediatric PMR is following:

Conduct a trial to evaluate pharmacokinetics, pharmacodynamics, and safety in pediatric patients of age 1 month to 16 years. The trial will include a minimum of 50 patients with solid tumors without bone marrow involvement in an open-label study and will include pharmacokinetic and pharmacodynamic sampling of tbo-filgrastim. Age groups to be included in the trial: Infants 1-24 months, Children 2-12 years, Adolescents 12-16 years.

10. Other Relevant Regulatory Issues

The application complied with financial disclosure requirements.

During the first review cycle, the Office of Scientific Investigations (OSI) determined that there were multiple times where there was unlocking and unblinding of the database. After extensive investigation and multiple correspondence with the Applicant and contract research organization, (b) (4) OSI has concluded that the observations noted on field examination were not likely to impact data integrity and that the data submitted appear reliable.

There are no other unresolved relevant regulatory issues.

11. Labeling

The labeling was reviewed by all disciplines and consultant staff. A Proprietary name has not been established. The proper name is tbo-filgrastim.

12. Decision/Action/Risk Benefit Assessment

- Recommended regulatory action: Approval.

- Risk Benefit Assessment

The risk benefit assessment suggests that tbo-filgrastim is effective to reduce the duration of severe neutropenia when compared to placebo and is associated with few attributable adverse events (bone pain).

Efficacy was demonstrated in a large, international, multicenter, randomized controlled trial randomizing 350 patients with breast cancer (Stage II to IV) receiving initial chemotherapy to XM02, a non-US-approved filgrastim product, and placebo treatment. The primary efficacy endpoint was the duration of severe neutropenia. The results revealed a statistically significant difference ($P < 0.0001$, X^2) in mean duration of severe neutropenia in cycle 1 between the XM02 arm (mean duration 1.1 days) and placebo arm (mean duration, 3.8 days). The Risk-benefit profile was also discussed in several reviews including the reviews of Drs. Farrell, Deisseroth and Herndon. The review team recommends approval of this BLA, and I concur.

- Recommendation for Postmarketing Risk Management Activities

A REMS is not recommended; however, routine post-marketing surveillance is recommended.

- Recommendation for other Postmarketing Study Requirements (PMR)/Commitments (PMC)

See action letter.

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/s/

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08/29/2012

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08/29/2012