CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-387

OTHER REVIEW(S)

Project Manager Overview

NDA 22-387 (pulmonary arterial hypertension)
TYVASO® (treprostinil) Inhalation Solution
Pharmacologic Class: Prostacyclin Analogue
Combination Product: Drug + Device
Chemical Classification: New formulation (chemical type 5)
Orphan Designation

Background:

Remodulin® (treprostinil) for subcutaneous (NDA 21-272) and intravenous (NDA 21-272/s-002) administration was originally approved under Subpart H on May 21, 2002 (NDA 21-272) and November 24, 2004, respectively.

The sponsor of Remodulin, United Therapeutics, submitted a New Drug Application (NDA) for Tyvaso® (treprostinil) Inhalation Solution 0.6 mg/mL (supplied as 2.9 mL ampules) on June 30, 2008. The studies were conducted under IND 70,362. The sponsor *proposed* to market the product for treatment of pulmonary arterial hypertension (WHO Group I) in patients with NYHA Class III — symptoms (same indication as Remodulin); however, the agreed upon indication will include use in Class III only. b(4)

The dosage and administration section of the labeling proposes four separate inhalation sessions per day (while awake). Each breath is expected to deliver a dose of approximately 6 mcg per breath. Initial treatment would begin with three breaths (18 mcg) and the maximal target dose per session is 54 mcg (9 breaths).

The Tyvaso Inhalation System involves use of a never-before cleared/marketed nebulizer device. The device, known as the Optineb IR, a portable ultrasonic nebulizer, was submitted under the NDA. DCRP consulted CDRH including a bioengineer and a human factors analyst.

The Division reviewed this NDA under the Good Review Management Principles and Practices—the NDA was assigned a Standard review (10-month clock), however, a 3-month clock extension was granted based on submission of new information related to the device.

Note that the sponsor plans to implement what appears to be an extensive hands-on training program for patients receiving the Tyvaso Inhalation System (drug/device) where nurses train patients one-on-one either in a clinic setting or at the patient's home. Also, patients will be able to obtain the product only from specialty pharmacies (i.e., the product is not available through typical pharmacy distribution channels).

NDA Reviews and Memos

Division Director's Memo #2
Dr. Norman Stockbridge; July 28, 2009
In his second memo, Dr. Stockbridge recommends approval.

Division Director's Memo #1
Dr. Norman Stockbridge; April 25, 2009
In Dr. Stockbridge's initial DD memo, he recommended a Complete Response based on issues relating to manufacture of the drug substance (facility inspections), biocompatibility of the

nebulizer parts that come into human contact, and device-related problems. Although a Complete Response action was recommended, in response to the Division's request, the sponsor submitted several amendments late in the review cycle (March/April) that, per the Division's decision, triggered a 3-month clock extension. Therefore, no action had been taken with respect to the original PDUFA goal date, April 30, 2009. Adding three months to the PDUFA clock made the new goal date July 30, 2009.

CDTL Memo #2
Dr. Avi Karkowsky; July 27, 2009
Dr. Karkowsky notes that there are problems with the device, however, many of the identified problems will be addressed through PMC 2, 3, and 4 (see approval letter). To address the inadequacies, the Division and the sponsor agreed to a timeline (see action letter) which would allow for marketing of the current version of the device for some period of time (i.e., < 2 years). Given his concerns for pulmonary toxicity based on human and animal data provided in the NDA, Dr. Karkowsky requested that the sponsor capture and track adverse events related to pulmonary toxicity via a postmarketing requirement (PMR).

CDTL Memo #1
Dr. Avi Karkowsky; April 19, 2009
Dr. Karkowsky recommended a complete response for various reasons, some of which are:

- The device seems complex and cumbersome to assemble, use and clean
- An adequate human factors study had not been completed (see CDRH's review)
- Biocompatibility data had not been submitted/reviewed
- Inspection facilities had not received an overall acceptable recommendation
- The benefit (increase in 6MWD) was relatively small and wanes at the interdosing interval; he also does not think the inhaled route should be automatically substituted for the SC/IV route of administration

Clinical Review; April 3, 2009
Dr. Avi Karkowsky
Recommended Action: Approvable (pending issues identified in CDTL memo)
Dr. Karkowsky emphasizes that Tyvaso was studied in patients on background therapies including sildenafil and bosentan and such information should be included in the indications section of the labeling. Furthermore, the waning of the treatment effect during the interdosing interval should be noted as well. His major concern regarding safety included adverse events related to irritation of the oro-nasopharynx and respiratory tree.

QT Study; January 30, 2009
Interdisciplinary Review Team for QT Studies
The study failed to exclude a 10 ms increase in the QTc interval (results below).

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Treprostinil sodium (54 mcg and 84 mcg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcF (ms)	90% CI (ms)
Treprostinil sodium 54 mcg	0.083	6.4	(3.5, 9.4)
Treprostinil sodium 84 mcg	0.083	8.5	(5.8, 11.3)
Moxifloxacin 400 mg*	3	8.2	(5.8, 10.7)

* Multiple endpoint adjustment is not applied. The largest lower bound after Bonferroni adjustment for 3 timepoints is 5.1 ms.

Statistical Review; April 7, 2009
Dr. John Lawrence
Dr. Lawrence notes that the primary endpoint of the study was change in exercise capacity at week 12 as measured by peak 6MWD. There was an approximately 20 m (95% CI 8, 33) difference between treatment and placebo in 6MWD (p=0.004). Looking across various subgroups, treatment effects appeared to be larger in the following subgroups of patients: those between 18-45 years of age; those whose baseline walk distances were in the bottom quartile (smallest baselines); and patients from the "rest of the world" (i.e., outside North America).

Clinical Pharmacology; March 24, 2009
Dr. Robert Kumi
Recommended action: Approval pending confirmation from CDRH on the reliability (precision and accuracy) that the device can deliver the dose reported in the PK studies.
In some studies, some subjects had undetectable or low treprostinil exposure compared to other subjects. The reason for these low exposures is unclear.

Pharmacology Review; June 24, 2008
Dr. Xavier Joseph
Recommended action: Approval

In his review, Dr. Joseph makes several recommendations for changes to the labeling but has no recommendations for additional nonclinical studies.

Chemistry Review #2; July 23/24, 2009
Dr. Monica Cooper
Recommended action: Approval
See review for details.

Chemistry Review #1; March 24, 2009
Dr. Monica Cooper
Recommended action: Complete Response because of pending issues as noted below.

1) All drug substance information is referenced to NDA 21-272 (Remodulin Injection). A supplement for a new treprostinil drug substance manufacturing facility and — process is currently pending (NDA 21-272/SCM-010). The previous treprostinil drug substance manufacturing site — was closed in 2006. Given that no other drug substance manufacturer is provided in this submission, the current NDA cannot be approved until the supplemental NDA 21-272/SCM-010 is approved. b(4)

2) An information request letter was sent to the applicant on 13-Jan-2009 outlining the CMC information needed to complete this application. The Amendment dated 25-Feb-2009 included a partial response to these issues. An in-use stability study of the drug product in the proposed Optineb nebulizer has not been completed and submitted for our review.

3) Evaluation of the Optineb nebulizer was consulted to CDRH. CDRH has not provided a recommendation at this time. However, an information request was sent to the applicant on 03-Mar-2009 that included several device issues. These issues are currently pending.

4) The Office of Microbiology has not provided a recommendation on the sterility assurance of the drug product.

The Office of Compliance has given an acceptable recommendation for the manufacturing and testing facilities.

Microbiology Review; March 24, 2009
Dr. John Metcalfe
Recommended action: Approval

DMEPA Review #2
In a review dated July 1, 2009, DMEPA found the proposed tradename, Tyvaso, acceptable.

DMEPA Review #1
In a review dated February 19, 2009, the Division for Medication Error Prevention and Analysis found that the proposed trade name Tyvaso does not appear to be vulnerable to name confusion that could lead to mediation errors.

Division of Scientific Investigations (DSI)
April 23, 2009; January 8, 2009
Two sites were inspected as part of a data audit in evaluation of this NDA:

- Numerous discrepancies were noted at Dr. McLaughlin's site and DSI did **NOT** consider the data to be reliable (OAI).
- Dr. Bourge appeared to have conducted the study adequately and DSI considered the data reliable from this site (NAI).

CDRH Review #2
Mr. Sugato De; Mr. Ron Kaye
Mr. De reviewed the biocompatibility information and found it acceptable; however, neither CDRH reviewer found the usability analysis and human factors study to be adequate. They also provide recommendations for changes to the proposed labeling.

CDRH Review #1
Mr. Sugato De; Mr. Ron Kaye
The reviewers in the Center for Devices and Radiological Health (CDRH) do not find the proposed device to be approvable (see review for details).

Action Items: An approval letter will be drafted for Dr. Stockbridge's signature. The approval letter will include one PMR related to pulmonary toxicity and three PMCs related to re-engineering of the device. Labeling, including the PI, PPI, and instructions for use (IFU), is being finalized.

by Dan Brum, Pharm.D., RAC
July 29, 2009

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