CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208276Orig1s000

SUMMARY REVIEW

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Divisional Memo

NDA: 208276 Remodulin (treprostinil) Implantable System for PAH.

Sponsor: United Therapeutics

Review date: 8 October 2016

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

This memo conveys the Division's decision not to approve this application.

This application has been the subject of reviews of CMC (Wong, Metcalfe, Williams, Zhao, McMichael, 27 July 2016), pharmacology/toxicology (Tesfamarian; 4 August 2016), clinical pharmacology (Lai; 21 September 2016), clinical (Gordon, Garnett; 3 August 2016), and statistics (Kong, 7 July 2016). There is no CDTL memo.

The system is a drug-device combination. The drug product is the same as was approved for infusion in 2002. The device is a central venous catheter and battery-operated implanted pump that is filled every (b) (4) weeks by syringe needle.

The original application was submitted in 2015, and the Division refused to file it (26 March 2015) because of problems with the reviewability of study data and identified device issues. The PMA was updated on 14 December 2015 and the NDA was resubmitted on 16 December 2015.

A multi-center study was conducted in 60 subjects to assess catheter-related complications. All were users of Remodulin with an external pump and a central catheter. The primary hypothesis being tested was whether the catheter-related complication rate was less than 2.5 per 1000 patient-days, a number derived from a review of the literature with use of the external pump.

These 60 subjects accumulated 44000 days of exposure, involving 1700 refills. During this period, there were 7 catheter-related complications in 4 subjects, ruling out (95% CI) a rate as high as 0.6 per 1000 days. These events were a procedure-related pneumothorax in one subject, two device dislocations in a second subject, one dislocation and two catheter punctures in a third subject, and venous stasis in a fourth subject.

There were 9 deaths during follow-up; all appeared to have been disease-related.

Three subjects had device-related infections (two sepsis, one local).

Ninety percent of subjects reported either site pain or site reactions.

Subjects had plasma levels of treprostinil obtained at baseline (on previous infusion modality) and then at 1 week. The mean change was 2.3%, with about 25% within-subject variability, which is similar to what is observed during oral treprostinil administration.

Pump accuracy decreases about 5% per year; most subjects had their doses increase during the study, but whether this represents compensation for pump performance or disease worsening is not clear.

6MWT was performed at baseline and 6 weeks, as were several patient-reported outcome measures, all of which seemed fairly stable.

The observed performance of the Remodulin Implanted System seems compatible with approval. The product quality team recommends against approval pending demonstration that m-creosol levels are adequate to control the risk of infection through refills. I concur.

In addition, the drug-device combination cannot be approved until the device is approvable. The PMA holder was notified of deficiencies, and the PMA was not approved by CDRH on 11 March 2016.

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/s/

NORMAN L STOCKBRIDGE
10/08/2016