CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-473

SUMMARY REVIEW

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memo

NDA: 22-473 Revatio IV (sildenafil citrate for pulmonary arterial hypertension)

Sponsor: Pfizer

Review date: 16 November 2009

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

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HFD-110/Brum

This memo conveys the Division's recommendation to approve Revatio IV (sildenafil) for treatment of pulmonary arterial hypertension in patients unable to take oral sildenafil.

This application has been the subject of reviews of CMC (Sapru 23 October 2009 and 16 November 2009), microbiology (Langille 2 November 2009), pharmacology and toxicology (Papoian 24 March 2009), clinical pharmacology (Brar and Zhao 16 October 2009), and medical (Gordon 28 October 2009).

Most issues have been addressed in Dr. Mehta's CDTL memo (13 November 2009). I summarize very briefly.

Sildenafil was approved for pulmonary arterial hypertension originally to improve exercise. I asserted that intravenous sildenafil had no role in patients unable to take oral sildenafil, because such patients were also unlikely to be ambulatory. When sildenafil was subsequently approved to delay clinical worsening, a niche for intravenous sildenafil was created, and I did not believe that it was necessary for approval of the intravenous product to demonstrate the harm of being off sildenafil therapy. Instead, the sponsor was tasked to identify an intravenous regimen that would give similar exposure and effect as the 20-mg oral dose.

Oral bioavailability is about 40%, so exposure (AUC) to the parent is about equal for 20 mg oral and 8 mg IV. However, exposure to the major active metabolite is less after IV, so 10 mg IV gives PDE5 inhibition closer to that seen with 20 mg oral administration, and this is the recommended dose. (IV dosing can also be expected to avoid or mitigate some CYP 3A drug interactions seen with oral administration.)

The sponsor originally proposed [redacted], but we concluded that this created a temptation for multiple use. Lesser filling would have resulted in a change in the volume-to-headspace ratio with unknown consequences on stability. Action was delayed while the sponsor developed some stability data with [redacted] mL vials containing 12.5 mL of 0.8 mg/mL sildenafil (=10 mg). Together with supporting data from the [redacted] vials, the CMC reviewer finds the existing data sufficient to support a 36-month expiry date. b(4) b(4)

All team members concur on approvability.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22473	ORIG-1	PFIZER INC	REVATIO

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/s/

NORMAN L STOCKBRIDGE
11/16/2009