

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-332**

**OFFICE DIRECTOR MEMO**



## DIVISION OF CARDIO-RENAL DRUG PRODUCTS

### *Divisional Memo*

**NDA:** 22-332 (Adcirca; tadalafil for PAH)

**Sponsor:** Lilly

**Review date:** 9 May 2009

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

**Distribution:** NDA 22-332  
HFD-110/Brum/Marciniak

This memo conveys the Division's recommendation to approve tadalafil for improvement in exercise in patients with pulmonary arterial hypertension (PAH).

Most issues have been addressed in Dr. Marciniak's CDTL memo (20 April 2009). I summarize very briefly.

Tadalafil is a PDE5 inhibitor, the second to be approved for PAH.

The CMC reviewer (Klein; 10 March 2009) finds the proposed 20-mg tablet (which is very similar to the marketed Cialis tablet) to be acceptable with a 36-month expiry.

The pharmacologist (Koerner; 6 March 2009) reports on one newly conducted proof-of-concept study in an animal model of PAH. The proposed chronic use is supported by previously conducted and reviewed studies of carcinogenicity and reproductive toxicity.

The clinical pharmacologist and pharmacometrician (Younis/Krudys; 27 March 2009) describe steady-state kinetics within about 5 days, with exposure at the highest dose studied, 40 mg, about 1.5 times the exposure at 20 mg. There is a clinically irrelevant decrease in exposure by concomitant bosentan, and a clinically irrelevant increase in exposure to bosentan. There are no interactions with digoxin or warfarin. There is a substantial decrease in exposure to ethinylestradiol, but not to levonorgestrol. Exposure to tadalafil only increases about 2-fold in patients with end-stage renal disease, and there is little impact of moderate hepatic impairment.

The medical and statistical reviewers (Gordon/Freidlin; 30 March 2009) focus mainly on study LVGY, a 16-week, parallel, placebo-controlled study of 6MW in 406 subjects (WHO Group I; ½ from US; ½ on bosentan; WHO functional classes II [32%] and III [65%]) randomized to doses of 2.5 to 40 mg. These data find most compelling evidence of effectiveness on 6MW in the 40-mg group, and somewhat less compelling evidence of effectiveness at 20 mg. Exact results depend on how missing data are handled; the sponsor's plan to impute worst-rank for death or worsening PAH and zero for other adverse events was reasonable. Pulmonary vascular resistance decreases with dose to 40 mg, but headache and flushing probably limit dose. The treatment effect of about 30 m is pretty typical; the overall result is driven by the US centers (for once).

There is a trend for a decrease in a composite end point of clinical worsening by dose, but whether it is statistically significant depends upon handling of a few ambiguous cases;

\_\_\_\_\_ and the reviewers find that approach to be generally reasonable.

b(4)

*Divisional memo  
Adcirca (tadalafil)*

*NDA 22-332  
Pulmonary artery hypertension*

Although the clinical pharmacologist and pharmacometrician recommend a 20-mg starting dose, I agree with Dr. Marciniak that starting at 40 mg is reasonable, dropping back to 20 mg, if necessary for tolerability.

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Norman Stockbridge  
5/15/2009 02:56:36 PM  
MEDICAL OFFICER