

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-332

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review Memo

Date	April 20, 2009
From	Thomas A. Marciniak, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 22-332
Supp #	
Proprietary / Established (USAN) names	Adcirca™ / tadalafil
Dosage forms / strength	Oral tablets / 20 mg
Proposed Indication(s)	Treatment of WHO Group 1 pulmonary arterial hypertension
Recommended:	Approval

1. Introduction to Review

Tadalafil is an orally administered phosphodiesterase (PDE) 5 inhibitor approved as Cialis in 2003 for the treatment of erectile dysfunction (ED). Another PDE 5 inhibitor, sildenafil, was approved for the treatment of pulmonary arterial hypertension (PAH) in 2005. This submission seeks approval of tadalafil for PAH under the tradename Adcirca.

2. Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Status

As noted in the primary clinical review, we granted orphan status for the PAH indication, agreed to considering one study acceptable, and issued a pediatric Written Request.

3. CMC/Microbiology/Device

The CMC reviewer, Dr. Donald N. Klein, recommends approval from a CMC perspective. He notes that the Adcirca tablet (20 mg) specifications are identical to the approved Cialis (tadalafil) tablet (20 mg) specifications with the exception of the appearance specification (the debossment and film coating color differ) and the deletion of the _____ (Karl Fischer) specification. Regarding the latter, the sponsor is _____

_____ A 36 month expiry is granted based on the stability results. Three drug product sites were recommended as acceptable by the Office of Compliance. The one outstanding issue (although not an approvability issue) is that, while the proposed dosage is 40 mg once daily, the sponsor only intends to market a 20 mg tablet.

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4. Nonclinical Pharmacology/Toxicology

4.1. General nonclinical pharmacology/toxicology considerations (including pharmacologic properties of the product, both therapeutic and otherwise).

The Division pharmacology and toxicology reviewer, Dr. John Koerner, recommends approval from a nonclinical pharmacology and toxicology perspective. As he notes,

Division agreed in a Pre-NDA meeting on January 15, 2008, that the nonclinical overview based on the ED application, along with a newly submitted nonclinical pharmacodynamic study showing efficacy in a rodent pulmonary hypertension model, provides sufficient nonclinical information for the present application. The relationship between PDE5 inhibition and free plasma tadalafil concentrations (C_{\max} free) in healthy human subjects suggests that inhibition of PDE5 was complete following oral doses of 10, 20 and 40 mg/day, i.e., the doses should be indistinguishable, at least at C_{\max} . The same analysis performed with free plasma drug levels in patients given sildenafil suggests that PDE5 inhibition was incomplete at the approved dose of 20 mg TID and even higher doses up to 80 mg TID. Since free plasma drug levels may not accurately reflect drug concentration at the site of action, this analysis should be evaluated cautiously.

The only additional nonclinical study included with this submission is a study evaluating the effects of tadalafil in a rodent model of pulmonary hypertension. In this study, tadalafil (10 mg/kg/day PO) was efficacious in rats with monocrotaline-induced pulmonary hypertension, both when given prior to, and after, development of pulmonary hypertension. Tadalafil had both functional and mortality benefits in this model, similar to the concurrent positive control, sildenafil (25 mg/kg/day PO). As the maximum recommended human dose is higher for the pulmonary hypertension indication than for the ED indication, animal to human exposure ratios need to be changed from the ED label.

4.2. Carcinogenicity

The sponsor did not perform additional carcinogenicity studies for this new indication of an approved drug. For the original approval in ED, submitted preclinical studies documented that tadalafil is not mutagenic and not carcinogenic in rats and mice.

4.3. Reproductive toxicology

The sponsor did not do additional reproductive toxicology studies for this new indication of an approved drug. For the original approval in ED, submitted preclinical studies documented that tadalafil had no effects upon fertility, reproductive performance, or reproductive organ morphology in rats and mice. In dogs there was treatment-related non-reversible degeneration and atrophy of the seminiferous tubular epithelium in the testes in 20-100% of the dogs that resulted in a decrease in spermatogenesis in 40-75% of the dogs at doses of ≥ 10 mg/kg/day. Systemic exposure (based on AUC) at no-observed-adverse-effect-level (10 mg/kg/day) for unbound tadalafil was similar to that expected in humans at 20 mg/day.

4.4. Other notable issues

There are no other notable nonclinical pharmacology or toxicology issues.

5. Clinical Pharmacology/Biopharmaceutics

5.1. General clinical pharmacology/biopharmaceutics considerations, including absorption, metabolism, half-life, food effects, bioavailability, etc.

The clinical pharmacology reviewer, Dr. Islam R. Younis, considers the NDA acceptable from a clinical pharmacology perspective with one notable deviation from the proposed labeling: He recommends that the starting dose of tadalafil in patients with pulmonary arterial hypertension should be 20 mg. The dose can be increased to 40 mg if deemed necessary based on patient's and physician's assessment of effectiveness. Dr. Younis' summary of the clinical pharmacology of tadalafil is the following:

Absolute bioavailability of tadalafil following oral dosing has not been determined. Tadalafil is highly distributed into tissues with mean apparent volume of distribution of 77 L. Tadalafil is highly bound to plasma proteins (94% bound). Tadalafil T_{max} is achieved between 2 and 8 hours (median time of 4 hours) after single oral-dose administration. The mean oral clearance for tadalafil is 3.4 L/hr and the mean terminal half-life is 15 hours in healthy subjects. Tadalafil is excreted predominantly as metabolites, mainly in the feces (approximately 61% of the dose) and to a lesser extent in the urine (approximately 36% of the dose).

Tadalafil is predominantly metabolized by CYP3A4 to a catechol metabolite, which undergoes extensive methylation and glucuronidation to form the methylcatechol and methylcatechol glucuronide conjugate, respectively. The major circulating metabolite is the methylcatechol glucuronide. Methylcatechol concentrations are less than 10% of glucuronide concentrations. In vitro data suggests that metabolites are not expected to be pharmacologically active at observed metabolite concentrations.

Over a dose range of 2.5 to 20 mg, tadalafil exposure (AUC) increases proportionally with dose in healthy subjects. Between 20 to 40 mg, an approximate 1.5-fold greater AUC is observed indicating a less than proportional increase in exposure over the entire dose range of 2.5 to 40 mg. During tadalafil 20- and 40-mg once-daily dosing, steady-state plasma concentrations are attained within 5 days, and exposure is approximately 1.3-fold higher than that after a single dose.

COMMENT: While the clinical pharmacology summary states AUC increases by only 1.5 fold from 20 to 40 mg, the data suggest an increase of about 1.9. I address the issue of the appropriate dosage in Section 7.1.6.

5.2. Drug-drug interactions

Tadalafil has several interactions that are noted in the approved labeling for ED:

- Tadalafil interacts with nitrates and with alpha blockers to lower blood pressure. Tadalafil is contraindicated for use with nitrates and has a warning regarding use with alpha blockers.
- Tadalafil also has labeling that CYP3A4 inhibitors increase its exposure and inducers decrease its exposure.

To supplement these drug interactions noted in the ED labeling, the sponsor performed three drug interaction studies relevant to PAH use:

- Bosentan at steady state significantly reduces tadalafil AUC_{0-24} by 42% and C_{max} by 27%. Tadalafil significantly increases C_{max} of bosentan by 20% and has no significant effect on bosentan AUC_{0-24} .
- Tadalafil did not alter the steady state PK of digoxin.
- Regard oral contraceptives, tadalafil at steady state significantly increased ethinylestradiol $AUC_{0-24,ss}$ by 25% and $C_{max,ss}$ by 70%, reduced ethinylestradiol-sulfate $AUC_{0-24,ss}$ by 71% and $C_{max,ss}$ by 63%, and did not alter the steady state systemic exposure ($AUC_{0-24,ss}$ and $C_{max,ss}$) of levonorgestrel.

It is worth noting that, per the ED label, tadalafil did not affect warfarin PK or INR effects.

5.3. Pathway of elimination

The sponsor did not perform additional metabolic pathway studies for this new indication of an approved drug.

5.4. Demographic interactions/special populations

In patients with pulmonary hypertension not receiving concomitant bosentan, the average tadalafil exposure at steady-state following 40 mg was 26% higher when compared to those of healthy volunteers. Per the tadalafil ED label, tadalafil exposure (AUC) in subjects with mild or moderate hepatic impairment (Child-Pugh Class A or B) was comparable to exposure in healthy subjects when a dose of 10 mg was administered. There are no available data for doses higher than 10 mg of tadalafil in patients with hepatic impairment. Insufficient data are available for subjects with severe hepatic impairment (Child-Pugh Class C). In clinical pharmacology studies using single-dose tadalafil (5 to 10 mg), tadalafil exposure (AUC) doubled in subjects with mild (creatinine clearance 51 to 80 mL/min) or moderate (creatinine clearance 31 to 50 mL/min) renal insufficiency. In subjects with endstage renal disease on hemodialysis, there was a two-fold increase in C_{max} and 2.7- to 4.1-fold increase in AUC following single-dose administration of 10 or 20 mg tadalafil. Exposure to total methylcatechol (unconjugated plus glucuronide) was 2- to 4-fold higher in subjects with renal impairment, compared to those with normal renal function. There are no adequate and well controlled studies of tadalafil use in pregnant women.

5.5. Thorough QT study or other QT assessment

The sponsor did not perform additional QT studies for this new indication of an approved drug. A thorough QTc study submitted for the original indication in ED was negative for QTc prolongation by regulatory standards.

5.6. Other notable issues

There are no other notable clinical pharmacology or biopharmaceutics issues

6. Clinical Microbiology

Tadalafil is an oral non-antimicrobial drug for which there are no clinical microbiology concerns.

7. Clinical/Statistical

7.1. Efficacy

7.1.1. Dose identification/selection and limitations

The sponsor studied a reasonably wide range of doses (2.5 to 40 mg daily) in the pivotal phase III study. The sponsor bases the dose proposed to be marketed upon efficacy results in the pivotal study, noting that only the highest dose 40 mg won on the primary endpoint by the pre-specified criteria. The primary statistical and clinical reviewer's agree with the sponsor's proposal. However, the FDA clinical pharmacology reviewer recommends a starting dose of 20 mg based on analyses of the time course of the primary endpoint.

COMMENT: I address the dose issue in Section 7.1.6.

7.1.2. Studies essential for approval

The current submission included seven clinical studies: one pivotal clinical trial; a long term, open-label extension study for safety; three drug-drug interaction studies; one food effect study, and a PK study in Japanese subjects. The pivotal trial also included a population PK substudy.

The pivotal trial LVGY was a typical PAH drug, randomized, double-blind, placebo-controlled study in patients with WHO Group I PAH using 6-minute walk distance (6MWD) as the primary endpoint. Entry criteria on right heart catheterization were a resting mean PAH of ≥ 25 , pulmonary artery wedge pressure ≤ 15 mm Hg, and pulmonary vascular resistance ≥ 3 Wood units. Patients aged 12 or older could be enrolled with a baseline 6MWD of 150-450 m and any WHO Class. Stable baseline use of bosentan was allowed. This was an international study with 82 sites in North America, Western Europe, and Japan. The sponsor stratified by PAH etiology,

bosentan use, and 6MWD \leq or $>$ 325 m and randomized 1:1:1:1 by IVRS to placebo, 2.5, 10, 20, or 40 mg tadalafil daily for 16 weeks.

The 6MWDs were performed at 4-week intervals to provide endpoint data in the event of dropouts (estimated at 10%). There was one variation: The protocol specified that patients should delay taking study drug on the day of the week 12 visit until after PK sampling and the 6MWD in order to obtain values at trough drug levels. While the protocol did not specify the timing of the 6MWDs at other visits, they were performed after the morning taking of study drug.

Ultimately 406 patients were randomized, about 49% in the US, and about 53% receiving bosentan. Median age was 54 with 78% female and 80% white. About 56% were idiopathic PAH, with the remainder predominantly secondary to connective tissue disorders. About 65% were WHO Class III, 32% Class II, and only 1% Class I and 2% Class IV. The small group sizes and three-level stratification did lead to some slight imbalances in baseline characteristics as shown in Table 1.

Table 1: Baseline Characteristics in Study LGVY

dose:	0	2.5	10	20	40
age, mean	55.0	54.3	53.7	52.8	52.6
age, median	54.4	57.6	53.1	53.6	52.7
male, %	21%	22%	16%	24%	25%
white, %	88%	80%	80%	75%	81%
black, %	9%	9%	10%	10%	5%
Asian, %	4%	11%	6%	11%	10%
WHO class III, %	68%	60%	68%	66%	65%
WHO class IV, %	2%	4%	2%	0.0%	0.0%
6MWD, mean m	343	347	336	338	352
6MWD, median m	363	360	355	353	380

There were 357 subjects who had been enrolled in LVGY who entered the open label extension trial LVGX. Of these 357 subjects, 352 received tadalafil (62 received 20 mg and 290 received 40 mg). A total of 266 subjects had at least 6 months exposure to tadalafil and 82 subjects had at least 12 months exposure.

7.1.3. Other studies

Please see Section 5 for a summary and the FDA clinical pharmacology review for the details of the other studies.

7.1.4. Primary clinical and statistical reviewers' findings and conclusions

Dr. Maryann Gordon, the primary clinical reviewer, and Dr. Valeria Friedlin, the primary statistical reviewer, summarized their efficacy findings as follows:

In the evaluation of its efficacy in PAH, tadalafil 40 mg once daily, compared to placebo, was shown to significantly increase mean walking distance. The placebo

subtracted treatment effect for subjects randomized to tadalafil 40 mg was 33 meters (95% confidence interval: 15 to 50 meters, $p < 0.001$). This effect on exercise is similar to those seen with many other PAH treatments approved for increasing exercise tolerance. Doses of tadalafil other than 40 mg were not found to be significantly better than placebo in prolonging walk distance. Secondary endpoints including change in WHO functional class, time to clinical worsening, and change in Borg scale tended to show numerical but not statistically significant improvement with the 40 mg dose compared to placebo. Those subjects in the tadalafil 40 mg group who were not taking bosentan had a treatment effect twice as large as those taking bosentan.

From clinical and statistical perspectives Drs. Gordon and Friedlin recommend approval. They have the following recommendations: The sponsor should be encouraged to evaluate higher doses of tadalafil in patients with PAH. The 40 mg once daily dose was the highest dose tested in this population and it was shown to be an effective dose in improving exercise tolerance only. The 20 mg once daily dose was marginally effective; doses lower than 20 mg had effects similar to placebo. There are no obvious dose-limiting serious adverse events. An interaction study with ambrisentan is recommended.

7.1.5. Pediatric use

While the inclusion criteria allowed enrolling down to age 12, only one patient in the pivotal trial was younger than 18. We did issue a Written Request for studies in children with PAH on November 16, 2006.

7.1.6. Discussion of notable efficacy issues

The one significant efficacy issue raised by the primary reviewers is whether the recommended dosage should be 20 mg or 40 mg. The clinical pharmacology reviewer recommends 20 mg rather than 40 mg as recommended by the sponsor and the primary clinical and statistical reviewers. The clinical pharmacology reviewer bases his recommendation on these observations:

- The median 6MWD change from baseline appears to be similar for doses 10, 20 and 40 mg.
- The maximum effect of tadalafil on 6MWD change from baseline and pulmonary vascular resistance is attained at tadalafil doses of 20 and 40 mg.
- There are dose-dependent adverse events, e.g., headache, flushing, and myalgia.
- The median 6MWD at Week 16 is not affected by concomitant bosentan administration, as long as the tadalafil dose is 20 mg or 40 mg.

The primary endpoint was 6MWD so scrutinizing the 6MWD results is critical for addressing this issue. While 6MWD is the usual primary endpoint for PAH trials currently, it has several limitations. There are problems with its determination, as shown by the 6MWDs for the following patient:|

Table 2: 6MWD by Visit for One Patient

week	6MWD
0	182.8
4	182.8
8	182.8
12	183
16	194

The fractional 6MWDs in Table 2 are explained by conversion from feet to meters (600 feet is about 182.8 m), but I think that it is highly unlikely that a patient would walk exactly 600 feet on four visits separated by 4 weeks each. Overall about 3.5% of subsequent 6MWDs were within 1 m of the preceding 6MWD.

PAH trials have another problem besides the type of endpoint: dropouts. I count that 17% of patients (17% placebo, 9% 40 mg) did not have a final 6MWD at 14 weeks or later. Because the effect size for tadalafil on 6MWD is less than 10%, how missing values are handled is critical to interpretation.

The protocol describes missing value handling as follows: “For subjects for whom it appears reasonable, prior to unblinding, to assume that the data are missing for reasons unrelated to disease state or treatment (e.g., on study but missing data because of visit outside of visit window), the last available 6-minute walk data will be used in the primary analysis. For subjects with study discontinuation attributed to treatment-related laboratory values or AEs (investigator-determined) in the absence of clinical worsening, a value of zero will be imputed for the change from baseline (i.e., no benefit from treatment) for missing data. For those subjects missing data due to death or disease worsening requiring discontinuation from study follow-up, ranks will be assigned as if the subjects in this group (made up of placebo and the active arm in the Pairwise comparison) had the lowest possible 6-minute walks. When descriptive statistics are calculated for 6-minute walk distance, subjects who die or discontinue follow-up due to disease worsening will be described with 6-minute walk distance treated as missing as well as imputed using the last available value (as is generally reported in the clinical literature).”

The protocol definition is reasonable except for one omission: It does not address how to handle patients who did poorly but then improved based on changes in treatment other than new PAH therapy (see definition of clinical worsening below), e.g., changed treatment for heart failure. Eight patients were hospitalized for heart failure and five continued on-study and completed a week 16 walk. While the sponsor either ignored these patients or included their final walk, I believe all must be counted as clinical worsening and have imputed worse values because any later improvement is likely related to change in heart failure treatment. Doing so I calculate the 6MWD changes from baseline to week 16 shown in Table 3.

Table 3: Reviewer's 6MWD Changes from Baseline to Week 16 in Study LGVY

dose	mean	median
0	0.6	7.5
2.5	12.5	13.4
10	16.9	28
20	20.9	30
40	32.0	30

One can appreciate the difficulty in assessing dose response from Table 3: By mean changes there is an apparent continuous dose-response; by median changes the response is flat at 10 mg and above. Hypothesis testing is more discriminating: The 40 mg dose clearly beats placebo regardless of the type of nonparametric analysis used, i.e., a nonparametric ANOCOVA including various baseline factors and covariates, e.g., the stratification factors, age, WHO class. The p values are typically 0.005 or lower. The 40 mg dose 6MWD improvement appears robust to different methods of imputing final values and different statistical analysis approaches. The 20 mg dose in the same analyses yields p values around 0.04. The latter value, while statistically significant by the usual criteria of 0.05, is not significant by the alpha level specified for the single study, i.e., 0.01.

Examining subgroup results is also helpful for understanding the effect of tadalafil on 6MWD. I show results by US vs. outside the US (OUS) in Table 4.

Table 4: Reviewer's 6MWD Changes from Baseline to Week 16 in Study LGVY by OUS vs. US

dose	mean		median	
	OUS	US	OUS	US
0	12.4	-14.4	16.5	-6.0
2.5	13.8	10.8	15	13.2
10	31.8	2.7	45	11.2
20	15.0	25.8	23	32.6
40	16.4	48.7	19	39.6

The results in the US appear more consistent and the 40 mg dose appears better than the 20 mg dose for both mean and median changes.

The results vary by bosentan use at baseline as shown in Table 6.

Table 5: Reviewer's 6MWD Changes from Baseline to Week 16 in Study LGVY by Bosentan Use

dose	mean		median	
	none	bosentan	none	bosentan
0	-16.1	14.4	0	15
2.5	8.5	16.2	15	9.5
10	14.1	19.6	35	19
20	22.0	19.9	32.0	30
40	33.8	30.4	25	32.1

Patients on placebo fare better with baseline bosentan use—I did note that for one patient the date of start of bosentan was the same as the study start date. While considering all patients the median 6MWD changes are not different for the 20 and 40 mg doses, they are for US patients as shown in Table 6.

Table 6: Reviewer’s 6MWD Changes from Baseline to Week 16 in Study LGVY by Bosentan Use, US Only

dose	mean		median	
	none	bosentan	none	bosentan
0	-26.8	-2.1	-18.9	1.3
2.5	-6.1	25.8	-10.0	21.7
10	-1.1	9.1	17.2	7.6
20	25.3	26.4	32.3	32.7
40	43.2	57.1	39.3	40.0

I examined 6MWD changes by other baseline factors and covariates (etiology, baseline walk, age, gender, race, WHO class) and did not find any consistent variations.

There is one additional 6MWD issue worth discussing: The week 12 6MWD was supposed to have been performed at trough while the other 6MWDs were performed after the morning dosing, so closer to peak. However, it is not clear how rigorously the walk timings were executed. The CRFs did capture the timing of the last dose for PK sampling purposes. If peak is defined as 1 to 8 hours after dosing and trough is defined as 16 to 32 hours after dosing, then at the week 12 visit about 66% of the walks (for those patients with timing data) were performed at trough for the 20 mg and 40 mg groups and at the week 16 visit 59% of the walks were performed at peak. Hence walk distances should not be compared between these two visits for the entire groups.

One possibility for comparing the week 12 and week 16 6MWDs is to compare the statistics only for patients having values (6MWD and timing) at both visits. I show such an analysis in Table 7.

Table 7: Reviewer’s Trough-Peak Comparisons for Change in 6MWD from Baseline for Patients Having Measurements at Both Week 12 (Trough) and Week 16 (Peak) in Study LGVY

dose	n	mean		median	
		trough	peak	trough	peak
0	25	23.3	18.9	9.8	12
2.5	30	21.5	28.5	28	15.2
10	33	38.1	38.4	24	21
20	24	39.7	36.4	30.4	27.8
40	26	30.2	40.8	24.5	40.7

There does not appear to be any suggestion of a peak effect except perhaps for the 40 mg dose. There does appear to be a slight dose response at peak.

COMMENT: There are several severe limitations to this analysis: The patients included are not randomized but selected on the basis of having successful walks at weeks 12 and 16. This selection bias is demonstrated by the increases in 6MWD in the placebo patients. The trough and peak values were not measured within a short timeframe and the peak follows the trough. The varying walk times, the long delay between trough and peak measurements, and the fixed order make assessments of trough-peak differences in this study difficult. That said, there does not appear to be a substantial difference in trough and peak 6MWDs and the changes in clinical worsening (see next) suggest the possibility of a sustained benefit.

Besides 6MWD the other endpoint worth scrutinizing is clinical worsening. The protocol defined clinical worsening as any of the following: death, lung transplantation, atrial septostomy, hospitalization due to worsening PAH, initiation of new PAH therapy (prostacyclin or analog, endothelin receptor antagonist, PDE5 inhibitor), or worsening WHO functional class. I have already mentioned above the problem with hospitalization due to heart failure—I believe such hospitalizations must be counted as due to worsening PAH and hence clinical worsening. Worsening WHO functional class is problematic because the determination of functional class is highly subjective. For example, one patient’s class was changed from II to IV at the last visit despite walking 462 m, 82 m better than baseline. This patient was counted as clinically worse. I noted several other similar cases and counted them as clinically worse only if there was other evidence for deterioration, i.e., walk deterioration or adverse events.

COMMENT: Most other trials define clinically worsening for WHO class deterioration as requiring a concomitant deterioration in 6MWD. However the latter is problematic if a 6MWD was not performed. I think that one should not use WHO class changes as indicative of clinical worsening unless other adverse events or use of additional therapy is noted. Additionally, investigators should record how they determined the WHO class. One problem may be that some patients may describe symptoms at rest but still can function adequately. Such patients are not class IV.

I show my tabulation of patients with clinical worsening events in Table 8.

Table 8: Reviewer’s Patients with Clinical Worsening Events in Study LGVY

dose	patients	%
0	12	15%
2.5	11	13%
10	9	11%
20	8	10%
40	5	6%

There appears to be a dose-response for reducing clinical worsening events. However, the time to first event comparing the 40 mg group to placebo is not statistically significant. Conversely, in logistic regressions of clinical worsening dose is a highly significant predictor regardless of what other baseline cofactors or covariates are included. However, the latter analyses were not specified prospectively.

There is one other notable efficacy issue: Tadalafil was studied almost exclusively in PAH patients in WHO Classes II and III. Other PAH drugs (but not sildenafil) have indication statements including WHO Class. Sildenafil, like tadalafil, was predominantly studied in WHO Classes II and III. The rationale for not mentioning WHO Class in the sildenafil label is that, unlike other PAH drugs, sildenafil has a favorable safety profile such that it is reasonable to try it for symptomatic benefit regardless of WHO Class studied. This rationale applies to tadalafil as well.

COMMENT: While the 6MWD changes in the whole study do not clearly differentiate the 20 mg from the 40 mg dose, they do for the US subgroup. The clinical worsening events also suggest that 40 mg may be more efficacious than 20 mg. While adverse events such as myalgia and flushing appear to be clearly dose-related, they were not serious and lead to few discontinuations. The clinical pharmacology reviewer makes some good arguments regarding recommending a starting dose of 20 mg, I agree with the clinical and statistical reviewers that, given the US and clinical worsening results, the appropriate starting dose is 40 mg. One can always fall back to 20 mg if adverse effects are intolerable. The clinical and statistical reviewers also recommend a post-marketing commitment to study higher doses. While this recommendation is reasonable, given the adverse event rates with 40 mg I do not consider such a study to be a requirement.

7.2. Safety

7.2.1. General safety considerations

Tadalafil is a marketed drug with extensive worldwide exposure for the ED population. It has shown excellent post-marketing safety, although there are some rare but unusual adverse reactions that have been associated with it: non arteritic ischemic optic neuropathy and sudden hearing loss.

7.2.2. Safety findings

Pertinent observations from the primary clinical review by Dr. Gordon are the following:

- Commonly reported adverse events (AEs) in the PAH studies such as headache, myalgia, back and extremity pain were similar to those in the ED population.
- There was no evidence of dose-related serious adverse events (SAEs).
- Dosing at 40 mg daily in PAH patients was tolerated by most subjects through one year in the uncontrolled long term safety study.
- The PAH studies did not reveal any new AEs.

- Dyspepsia and liver enzyme elevations were more frequent in the patients also taking bosentan.

Because some AEs such as myalgia are described variously by different patients and investigators, I recoded some AEs to be inclusive of all reasonable variations. I show my rates of patients with selected dose-related AEs in Table 9.

Table 9: Reviewer's Rates of Selected Dose-Related AEs in Study LGVY

dose:	0	2.5	10	20	40
dyspepsia	6%	6%	6%	17%	18%
flushing	5%	9%	9%	9%	16%
headache	17%	18%	37%	33%	43%
myalgias*	6%	7%	9%	17%	27%

*including muscle cramping

Please see the primary clinical review for numeric summaries of other AE rates.

COMMENT: While no SAEs were clearly dose-related, the common AEs were, including headache, myalgia, flushing, pain in extremity and back, nausea, vomiting, and dyspepsia. Please see also the table of adverse event reporting in Section 7.1.5 of the primary clinical and statistical review. Some of these AEs (e.g., nausea, vomiting, dyspepsia, back pain, chest pain) do max out at 20 mg, although they have similar rates at 40 mg. At 40 mg some rates become substantial, e.g. headache 43% vs. 17% placebo, myalgias 27% vs. 6% placebo.

7.2.3. Safety update

The 120-day safety update included additional follow-up for two PAH studies, the uncontrolled LVGX extension study and an uncontrolled compassionate use study. The additional follow-up did not reveal any unique safety concerns. Please see the primary clinical review for summaries of the events reported.

7.2.4. Immunogenicity

Immunogenicity is not a significant concern for this approved drug.

7.2.5. Special safety concerns

The special safety concerns regarding non arteritic ischemic optic neuropathy and sudden hearing loss did not manifest themselves in the PAH studies. The PAH studies did not produce any additional special safety concerns.

7.2.6. Primary reviewers' comments and conclusions

The primary reviewer provided the summary of her findings as noted in Section 7.2.2 above. She recommends approval based on the efficacy and safety findings.

11.4. Patient labeling/medication guide

Patient labeling will be discussed after the physician label is finalized.

12. DSI Audits

DSI inspected one site for the pivotal study and, some minor protocol violations notwithstanding, considered the data to be acceptable.

13. Conclusions and Recommendations

13.1. Recommended regulatory action

I recommend Adcirca be approved for the treatment of WHO Group I pulmonary arterial hypertension in adults.

13.2. Safety concerns to be followed postmarketing

I have no safety concerns that need to be followed postmarketing.

13.3. Risk Minimization Plan

I do not recommend a risk minimization plan. There are no unusual or excessive risks for this product.

13.4. Postmarketing studies

I do not recommend any postmarketing studies. There are no concerning unanswered questions regarding this product.

13.5. Comments to be conveyed to the applicant

The proposed labeling changes will be discussed with the sponsor during label negotiations.

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