CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204819Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	9 September 2013
From	Norman Stockbridge
Subject	Cross-Discipline Team Leader Review/ Division Director memo
NDA/BLA # **Supplement#**	204819 000
Applicant	Bayer Healthcare
Date of Submission	8 February 2013
PDUFA Goal Date	8 October 2013
Proprietary Name / Established (USAN) names	Adempas Riociguat
Dosage forms / Strength	Oral tablets; 0.5/1/1.5/2/2.5 mg
Proposed Indication(s)	1. Improve exercise capacity and WHO functional class in patients with chronic thromboembolic pulmonary hypertension (CTEPH) 2. Improve exercise capacity, improve WHO functional class, and (b) (4) clinical worsening in patients with pulmonary arterial hypertension (PAH; WHO Group I)
Recommended:	Approval

Reference ID: 3369854

1. Introduction

Riociguat is a new molecular entity with a novel mechanism of action. There is no disagreement among the review team or the Advisory Committee on the appropriate regulatory action. This would be the first approval for a treatment for CTEPH.

2. Background

Riociguat works the same vasodilatory system as sildenafil does, and it has the same potential for amplifying the effect of nitric oxide.

Approval is based on single randomized, double-blind, placebo-controlled studies in CTEPH and PAH.

3. CMC/Device

I refer to the CMC review by Dr. Cooper (5 July 2013). There are no issues with regard to drug substance or drug product, and approval with a 36-month expiry is recommended. Establishment inspections are complete and satisfactory.

4. Nonclinical Pharmacology/Toxicology

I refer to Dr. Hausner's review (19 June 2013). Riociguat is a soluble guanylate cyclase stimulator. Riociguat is thought to stabilize binding of NO to cGMP. PDE5 inhibitors (like sildenafil) affect a later step in this pathway. Expected effects of riociguat were vasodilation and reductions in inflammation, fibrosis, and cellular proliferation. The vasodilation appears to be pretty general—pulmonary, systemic, and coronary.

In rats, there is thickening of the hypertrophic zone of femoral and tibial growth plates and increased thickness of trabeculae of the primary spongiosa[1]. Findings are less well described in several other studies. The sponsor and reviewer believe these findings are related to the cGMP mechanism of action. Whether they have any relevance to humans (particularly adults), is an open question, but nothing of concern has been seen in clinical studies of riociguat.

Our consultants in DBRUP[2] conclude that the signal is of no concern in adults and what concerns there may be in very young children should not preclude pediatric studies if otherwise indicated.

Riociguat was negative in genotoxicity assays and in rodent two-year carcinogenicity studies.

Riociguat caused some fetal loss (two species) that Dr. Hausner thinks is probably related to vasodilation effects. There was also an increase in VSDs at the highest dose tested in one species. These findings support a box warning and REMS.

5. Clinical Pharmacology/Biopharmaceutics

I refer to the review by Drs. Menon-Anderson, Marathe, Rogers and Zhao (1 July 2013).

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[1] See pages 174-187.

[2] Kehoe & Voss; 26 April 2013)

Most of the activity resides with the parent molecule. Absolute bioavailability is high and peak levels are obtained at around 5 hours in the target PAH population. Elimination is largely by CYP metabolism, prominently 1A1, which is up-regulated in smokers, so they require higher doses. Renal impairment doubles exposure. Antacids roughly halve exposure.

Most of the effect on 6MW is seen by a dose of 1.5 mg, but the data are inadequate to conclude whether 2.5 mg is more effective in most patients. Hypotension as an adverse event tends to increase with dose among patients with a baseline systolic blood pressure <110 mmHg, but it is not a very dramatic effect[3].

The only pharmacodynamic drug interaction of consequence is with nitric oxide (delivered in various forms), a trait it shares with PDE5 inhibitors.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

I refer to reviews by Drs. Lawrence (statistical; 1 July 2013) and Dunnmon (clinical; 8 July 2013). The phase 3 development program consists of two studies, one each in PAH WHO Group I—PATENT-1—and one in CTEPH—CHEST-1.

PATENT-1 was a double-blind, parallel design study in which 405 subjects with PAH[4] were randomized 4:1:2 to riociguat titrated between 1 and 2.5 mg TID, riociguat titrated between 1 and 1.5 mg TID, and placebo.

Subjects had idiopathic PAH (~60%), connective tissue disease (~25%), and a smattering of other etiologies. Most were Functional Class II-III at baseline. About 43% were on an endothelin receptor antagonist, and about 9% were on a prostacyclin.

The primary end point was distance walked in 6 minutes (6MW) evaluated by ITT as change from baseline to 12 weeks. Subjects who died or otherwise discontinued (~10%) had imputed values. The results for the larger target dose were highly statistically significant ($p<0.0001$). The mean effect was about 30 m, and "mean effect" seems to be a perfectly satisfactory way to describe the result, as shown by the cumulative distribution curve for 6MW[5]. The treatment is largely manifest by the first visit (week 2)[6]. The results are consistent across subgroups by demographics, disease severity, and geographical region[7]. There is no long-term withdrawal study, but the former placebo group improves and 6MW times seem stable during the 24-month open-label extension study[8].

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[3] See page 15.

[4] WHO Group I; PVR >300dyne·s·cm^{-5}; stable 6MW of 150-450 m.

[5] Lawrence; Figure 1.

[6] Dunnmon; page 112ff.

[7] Dunnmon; page 124.

[8] Dunnmon; page 127.

Statistical significance was achieved on ordered secondary end points of pulmonary vascular resistance, NT-proBNP, WHO Functional Class (p=0.003), time to clinical worsening[9] (p=0.005), and Borg dyspnea (p=0.002).

The clinical review and the clinical pharmacology review both question and address the small incremental benefit of doses above 1.5 mg TID. The arm in which the dose was capped at 1.5 mg has ¼ of the size of the 2.5-mg arm, limiting conclusions that can be drawn. Labeling should, I think, say that the incremental benefit is less than it is with the first 1.5 mg, but not discourage up-titration. In particular, I note that the PK variability is pretty high, even before considering such things as smoking that are identified as lowering exposure. Some people will need a dose of 2.5 mg or more to get the average response to 1.5 mg.

CHEST-1 was a double-blind, parallel design study in which 262 subjects with CTEPH[10] were randomized 2:1 to riociguat titrated 1 to 2.5 mg or to placebo and followed for 16 weeks.

Most subjects were WHO Functional Class II-III at baseline. About 10% were on other vasodilators, mostly prostacyclins.

The primary end point was 6MW. The primary analysis was ITT, and imputation was necessary for ~7% of subjects who failed to complete 16 weeks. The mean difference between groups was ~40 m (p<0.0001), and again the distribution of responses looks shifted to the right[11]. The difference between riciguat and placebo is seen on the first visit (week 2) and it increases with time on treatment. The results are consistent across subgroups by demographics, disease severity, and geographical region[12].

Statistically significant effects were found on ordered secondary end points of PVR, NT-proBNP, and WHO Functional Class (p=0.003). Borg was nominally significant but not reachable after time to clinical worsening failed[13] (p=0.17).

The PVR and BNP findings are of some interest mechanistically, although Dr. Lawrence shows that PVR explains little-to-no treatment effect on 6MW.

Both studies employed symptom scores EQ5D and LPH Questionnaire. LPH was nominally highly significant in PATENT-1, but not EQ5D. In CHEST-1, EQ5D was nominally highly significant, but not LPH. Effects were seen in both studies on WHO Functional Class.

8. Safety

Between the phase 3 studies and their long-term extensions, there is over 1200 patient-years of exposure to riociguat; the mean exposure is around 600 days.

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[9] All-cause mortality, heart/lung transplantation, rescue pulmonary endarterectomy, hospitalization for worsening PAH, initiation of new PAH therapy, confirmed 15% reduction in 6MW, or persistent deterioration to at least WHO Functional Class III.

[10] Inoperable or recurrent; PVR >300dyne·s·cm^{-5}; stable 6MW of 150-450 m.

[11] Lawrence; Figure 3.

[12] Dunnmon; page 90.

[13] There are only 9 clinical worsening events, so although the rate on riociguat is less than half what it was on placebo, the results are not close to significant.

There were five deaths in these studies on riociguat, the overall rate being lower on study drug than on placebo[14].

About 10% of subjects in the phase 3 blinded trials reported hypotension as an adverse event. Syncope was reported more commonly on placebo in both studies.

Anemia and bleeding were reported more commonly on riociguat than on placebo (4% vs. 0 in CTEPH, 2% vs. 0 in PAH).

Potential bone toxicity events were carefully assessed, including a consult to DBRUP. There is no excess of treatment-emergent pain events in either study.

Common adverse events include headache, dizziness, and dyspepsia in both studies, all consistent with other vasodilators.

Among continuous safety data analytes, the shift in blood pressure is clear, developing as plasma levels rise.

The sponsor's QT study ruled out an effect as large as 20 ms[15].

The sponsor proposed a REMS to minimize fetal exposure. The REMS includes a Medication Guide and Elements to Assure Safe Use—prescriber certification, pharmacy certification, and documentation of safe use conditions. Comments on this plan[16] were conveyed to the sponsor

9. Advisory Committee Meeting

An Advisory Committee meeting was held on 5 August 2013 to discuss the approvability of riociguat, dosing, and risk of hypotension. The Committee voted unanimously in favor of approval for both CTEPH and PAH, feeling that there was enough relevance of PAH to approve CTEPH on the basis of a single trial. There were no significant concerns about trial designs or execution. Hypotension did not appear to be markedly worse on riociguat than has been seen with other vasodilators. Risks of hypotension with use of nitric oxide donors and PDE5 inhibitors were felt to be adequately managed by labeling.

10. Pediatrics

PMHS concurred with the sponsor's waiver request as it relates to studying CTEPH (impracticable). PMHS and DBRUP both recommend not waiving for PAH. The Division concurs.

11. Other Relevant Regulatory Issues

DSI inspected 4 clinical sites of the phase 3 program and the sponsor. The data were considered reliable.

Financial disclosure information revealed no cause for concern.

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[14] Individual events on study drug and placebo are briefly described on pages 149 (CTEPH) and 151 (PAH) of Dr. Dunnmon's review.

[15] Dang, Zhang, Brar, Fiszman, & Krudys; 8 May 2013.

[16] Dunn; 19 July 2013.

DMEPA considers the tradename, Adempas, acceptable.

12. Labeling

See labeling appended to proposed action letter.

13. Recommendations/Risk Benefit Assessment

The Division, the review team, and the Advisory Committee support approval. Results are highly persuasive in two studies, and everyone appears to be comfortable with their mutual support for indications in PAH, where there are lots of successful predicates with vasodilators, and in CTEPH, where this would be the first product.

Of the safety concerns, I note the following:

- Vasodilatory adverse events are common to all of these drugs. Labeling suffices. I do not recommend restricting the dose. Riociguat's effects on 6MW are typical of vasodilators, perhaps 10-15% of the actual deficit and too small to be readily appreciated by individual patients. The dose should be allowed to range as high as 2.5 mg TID (as was studied), higher in patients with CYP 1A1 induction (smokers).
- Bone findings seem most likely pertinent to the use in small children. The pediatric development program should gather data in adolescents, and then work progressively into younger populations.
- Interactions with nitric oxide donors and with PDE5 inhibitors can be managed in labeling.
- The sponsor and the review team conclude that the teratogenicity findings are a sufficient basis for a REMS. I suppose it is, but the case seems pretty weak.

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/s/

NORMAN L STOCKBRIDGE
09/09/2013