Summary Review for Regulatory Action

Date	(electronic stamp)
From	Norman Stockbridge
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	NDA 21-290 S-012
Applicant Name	Actelion
Date of Submission	06 August 2007; resubmission 30 March 2009
PDUFA Goal Date	30 September 2009
Proprietary Name / **Established (USAN) Name**	Tracleer/ Bosentan
Dosage Forms / Strength	Tablets 62.5 and 125 mg
Proposed Indication(s)	1. PAH WHO Class II
Action:	*Approve*

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Gordon (19 March 2008; 05 June 2008)
Statistical Review	Bai (31 March 2008)
Pharmacology Toxicology Review	None
CMC Review/OBP Review	None
Microbiology Review	None
Clinical Pharmacology Review	None
DDMAC	Hubbard (10 April 2008; 06 April 2009)
DSI	None
CDTL Review	None
OSE/DRISK	Mills/Duckhorn (05 May 2009)
Other	None

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMETS=Division of Medication Errors and Technical Support
DSI=Division of Scientific Investigations
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

1. Introduction

Bosentan is currently approved to treat PAH in patients who are WHO functional class III-IV. With this supplement, Actelion seeks to have bosentan approved for use in patients with class II symptoms.

2. Background

The original development program for bosentan excluded patients with class II symptoms. Sildenafil and ambrisentan were both subsequently approved for use in patients with class II-IV symptoms.

3. CMC/Device

NA

4. Nonclinical Pharmacology/Toxicology

NA

5. Clinical Pharmacology/Biopharmaceutics

NA

6. Clinical Microbiology

NA

7. Clinical/Statistical-Efficacy

The proposed indication is supported by one new efficacy study, EARLY, conducted largely in Europe. Class II subjects (N=185; 16% on stable doses of sildenafil) were randomized evenly to placebo or to bosentan (62.5 mg BID uptitrated at 4 weeks to 125 mg BID) and followed for 6 months. The primary end point was the intersection of two components: percentage change in PA pressure and change in 6-minute walk distance (6MW), with both components to be tested at p=0.05. Early withdrawals had the last observation carried forward (LOCF) or were assigned 0 for 6MW (death) or were assigned worst rank (clinical worsening). Thus subjects having nonfatal hepatotoxicity had LOCF applied. There were 3 secondary clinical end

points—time to worsening, change in WHO class, and change in Borg Dyspnea score—and no plan for controlling type I error among them[1].

Imputation rules were applied to 6 subjects on placebo (5 of whom had worst value used because of clinical worsening) and 14 subjects on bosentan. Two of these had a worst value used, 5 had LOCF (withdrawals for hepatotoxicity), and 7 were dropped from analysis of 6MW for lack of any value to carry forward.

PAP was assessed in 88 of 92 on placebo and 80 of 93 on bosentan. There was a robust effect on PAP, about a 23% reduction ($p<0.0001$), nominally significant even in the small subset on background sildenafil. Since there is no known relationship between PAP and symptoms or progression of PAH, neither reviewer gives much weight to this finding.

6MW was assessed in 91 of 92 on placebo and 86 of 93 on bosentan. The change from baseline and placebo (double delta) was about 19 m from a baseline (bosentan) of 443 m ($p=0.076$). Thus, even with the sponsor's handling of missing data, this component of the primary end point was not statistically significant. In contrast to previous experience, subjects with a baseline 6MW above the median tended to have a greater treatment effect.

Clinical worsening appears to have been analyzed by counting no events among subjects withdrawn for any reason. Thus, worsening was counted for 13 subjects on placebo (1 death, 3 PAH hospitalizations, 12 progressions) and 3 subjects on bosentan (1 death, 1 hospitalization, 2 progressions). By time for first event, there was a 77% reduction in the risk of worsening ($p=0.011$). Counting the worsening cases only once by worst outcome, there was 1 death in each group, 3 hospitalizations on placebo and 1 on bosentan. Of the remaining Worsening cases, 8 subjects on placebo advanced to WHO class II or greater or had marked reductions in 6MW or both vs. 1 on bosentan.

WHO functional class was assessed in the same subjects with available 6MW data.

Table 1. Final WHO class (evaluable subjects)

	Placebo N=91/92	**Bosentan N=87/93**
I	5	6
II	74	78
III	9	1
IV	3	2

How the two distributions were to be compared is unclear; the proportion of subjects worsening in functional class was less on bosentan (sponsor's reported $p=0.02$).

Borg dyspnea was unaffected.

8. Safety

There was one death in each group. The death on bosentan does not appear to be related to treatment. Nine subjects in each group withdrew for adverse events. Six withdrawals from

[1] Indeed, the SAP denies any intent for formal testing of secondary end points.

bosenatan (and none on placebo) were for hepatotoxicity[2]. Five withdrawals on placebo (and one on bosentan) were for pulmonary hypertension.

9. Advisory Committee Meeting

NA

10. Pediatrics

NA

11. Other Relevant Regulatory Issues

There are no other issues.

12. Labeling

Labeling has been negotiated with the sponsor and all review team members.

13. Decision/Action/Risk Benefit Assessment

I concur with both reviewers that hemodynamic effects are not a compelling basis for approval. However, such effects probably underlie the mechanism of bosentan's effectiveness in treating PAH.

Both reviewers want to deny approval on the supplement on the basis that bosentan was not associated with statistically significant effects on the clinically relevant end point of 6MW. However, I am struck by the fact that other development programs have their indications encompassing functional class II patients on the basis of overall effects in a more comprehensive phase 3 study, with no more evidence than we have here that treatment is effective in the class II subgroup.

The nominal mean effect on 6MW was a net improvement by less than 5%, less than half of that seen with patients with higher functional class. Risk of hepatotoxicity is about the same as in the higher functional class patients. Thus, an argument can be raised that the benefit-risk difference is substantially lower here than in higher functional class patients, assuming, with $p=0.078$, that there is an effect here at all.

Ignoring issues of missing data and the intent to use secondary end points solely for exploratory purposes, there are nominally statistically significant ($p<0.05$) effects of bosentan on 5 hemodynamic secondary end points and 2 of 3 clinical end points. The one clinical end point of most interest—progression—was most persuasive of a beneficial effect, and it mostly reinforces the effects on 6MW and WHO functional class. No improvement is seen for mortality or disease-related hospitalization.

Balanced against any claims of benefits is the risk of hepatotoxicity, here about 13% at 6 months for clinically relevant AST or ALT elevation and about half of that for 8-fold

[2] All had >8-fold increases in AST or ALT. The proportion of subjects with >3-fold elevations was 13% on bosentan and 2% on placebo.

elevations. As Dr. Gordon has noted, you are about as likely to avert progression to a higher WHO functional class as you are to have significant hepatotoxicity. If the hepatotoxicity were irreversible, this would not be an acceptable trade, but, in the vast majority of cases, it is reversible. I am more concerned about the prospect that subjects experiencing hepatotoxicity at this early stage of their disease have lost the opportunity to obtain a greater benefit later in their disease.

Factoring in my prior expectations from effectiveness of other drugs in this class, effects of bosentan on exercise in more advanced disease, favorable hemodynamic effects seen here, and a favorable lean on exercise and symptoms (WHO functional class and "progression"), I conclude that bosentan very likely does have beneficial symptomatic effects in patients with WHO class II PAH.

The apparently small effect is not, in my opinion, commensurate with the risk of hepatotoxicity and the risk of being unable to use bosentan in later stages of PAH. However, the community may reasonably make a different conclusion, so I favor approval with labeling that warns what the tradeoff might be.

Approval was initially delayed (and then a Complete Response letter was issued 27 February 2009) because of an outstanding REMS commitment. That has now been resolved with S-016, which is also ready for approval.