



# Questions

bosentan  
10 August 2001

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Cardio-Renal Advisory Committee

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The Cardio-Renal Advisory Committee is asked to opine on the benefits and risks of bosentan, an endothelin receptor antagonist, for the treatment of primary and secondary pulmonary hypertension. Reviews of chemistry and statistics present no apparent barriers to its approval.

Bosentan carries safety risks with respect to teratogenicity, testicular toxicity, drug interactions, hepatotoxicity, and anemia. The Committee is asked if it believes these risks are offset by the benefits of treatment.

1. The two principal effectiveness studies assessed 6-minute walking distance and demonstrated effects favoring bosentan with p-values of 0.02 and 0.0002 individually.
  - 1.1 The prospective analysis plan included rules for handling the data from subjects who withdrew prior to the final assessment. How does the handling of early withdrawals affect the results?
  - 1.2 Six-minute walk was the primary end point in these studies, but there were other measures of clinical benefit.
    - 1.2.1 What is the role of secondary end points where the treatments are clearly distinguishable on the primary end point?
    - 1.2.2 If bosentan were to be approved, what should the label say are the effects of bosentan on the following parameters:
      - Mortality?
      - Hospitalization?
      - Disease progression?
      - Need for other drugs?
      - WHO functional class?
      - Borg dyspnea index?
      - Hemodynamics?
  - 1.3 Considering all pertinent data, is bosentan an effective treatment for pulmonary hypertension?
  - 1.4 Over what period of administration are the benefits of bosentan manifest?
  - 1.5 Over what dose range are the benefits of bosentan manifest?
2. Did the dose of bosentan rise steadily during treatment?
  - 2.1 If so, why? If not, would the studies have permitted one to see such a phenomenon?
  - 2.2 Are these data or the lack thereof an approval issue?
  - 2.3 If bosentan were approved, how should the label describe this?

3. Consider the following safety issues:
  - 3.1 Bosentan is a teratogen. Is this an approval issue for a treatment for pulmonary hypertension?
  - 3.2 Some endothelin receptor antagonists have shown testicular toxicologic findings in animal studies, usually in studies lasting 12 weeks or longer; this may be a class effect. The animal data for bosentan appear in the pharmacology review. There are no pertinent data in humans. If one were to conclude that bosentan exhibited testicular toxicology in animals, would this be an approval issue for a treatment for pulmonary hypertension? If so, what, prior to approval, would need to be known about ...
    - 3.2.1 ... effects in animals?
      - Time course for onset?
      - Relationship to dose?
      - Reversibility?
      - Other?
    - 3.2.2 ... effects in man?
      - Sperm counts and morphology?
      - Biopsy?
      - Other?
  - 3.3 Bosentan will affect the metabolism of many other drugs, and, because of induction, the effects will vary over time.
    - 3.3.1 Is this an approval issue for a treatment for pulmonary hypertension?
    - 3.3.2 If not, what can be done to minimize the hazards?
  - 3.4 Bosentan produced large increases in hepatic enzyme levels in a substantial number of subjects.
    - 3.4.1 Is it clear that hepatic toxicity is always reversible?
    - 3.4.2 Will instructions for frequent monitoring adequately address this risk?
  - 3.5 Bosentan produced substantial decreases in hematocrit in a substantial number of subjects.
    - 3.5.1 Is it clear that hematologic toxicity is always reversible?
    - 3.5.2 Will instructions for frequent monitoring adequately address this risk?
  - 3.6 The development program in pulmonary hypertension is small, limiting its ability to uncover safety risks with an incidence much below 1%.
    - 3.6.1 Are the safety data in the target population adequate to support approval?
    - 3.6.2 If not, are the additional data from other populations, e.g., normal volunteers or CHF patients, sufficient?
  - 3.7 Are there other safety issues?
4. Subjects whose disease progressed despite randomized treatment went on to receive another drug. Is it known that the benefits of the follow-on therapy are manifest after treatment with bosentan?
5. Should bosentan be approved for the treatment of pulmonary hypertension?