FOOD AND DRUG ADMINISTRATION

Center for Drug Evaluation and Research (CDER)

Arthritis Advisory Committee (AAC)

November 24, 2008

Questions to the AAC

1. Safety of febuxostat
   In its review of the two initial Phase 3 trials (Studies 009 and 010) of febuxostat 80 mg and 120 mg, the FDA found a larger number of APTC-defined cardiovascular thromboembolic events in the febuxostat arms compared to the active control allopurinol arm. In the subsequent Phase 3 trial (Study F-153) of febuxostat 40 mg and 80 mg the event rate for cardiovascular thromboembolic events was not increased with either febuxostat dose compared to the allopurinol control; however, the event rate in the control group was low.

   Please discuss:

   a) The strength of evidence suggesting a cardiovascular safety signal for the febuxostat 40 mg dose;

   b) The strength of evidence suggesting a cardiovascular safety signal for the febuxostat 80 mg dose

2. Appropriate dosing:
   In the two Phase 3 trials of febuxostat 80 mg and 120 mg, the serum uric acid was decreased more in the febuxostat arms than in the control arm. In the subsequent Phase 3 trial, febuxostat 40 mg met the primary endpoint of non-inferiority to allopurinol. The Applicant has proposed a dose regimen of 40 or 80 mg. Please discuss the efficacy and clinical utility of each dose.

3. Special populations:
   For patients with renal impairment it is recommended that the dose of allopurinol be reduced to avoid accumulation of the drug and its metabolites. This practice often limits the ability to achieve target levels of uric acid with the use of allopurinol.

   Please discuss:

   a) Whether patients with renal impairment represent an unmet medical need population for uric acid lowering therapies.

   b) The safety, efficacy and clinical utility of febuxostat in patients with renal impairment.

4. VOTE: Do you recommend approval of febuxostat for the treatment of chronic gout?

   If the answer is yes:

   a) What is the appropriate dose?

   b) What additional studies, if any, should be conducted postapproval to further assess the safety of the product?

   If the answer is no:

   a) What additional data are needed to gain approval?

   b) Is there an unmet medical need population for which febuxostat should be approved? Specifically consider:

      (1) Patients who have inadequate response to or are intolerant of currently available therapies

      (2) Patients with renal impairment