Food and Drug Administration

Center for Drug Evaluation and Research (CDER)

Arthritis Advisory Committee
June 2, 2004

Questions to the Committee

I. Please discuss the utility of serum uric acid as a surrogate marker for the chronic treatment of gout.

- If it is an appropriate surrogate, what level of serum uric acid or amount of change in serum uric acid level would be considered adequate evidence of efficacy?
- Would an analysis comparing the mean change in serum uric acid level for the treatment populations adequately reflect efficacy?
- Would an analysis comparing the number of individuals in each treatment arm reaching a prespecified level or amount of change adequately reflect efficacy?
- Are there advantages to choosing an analysis of either the uric acid levels at last visit or the uric acid levels over time (based on the area under the curve)?
- Does the choice of a surrogate as the efficacy endpoint influence the decision of what is considered acceptable risk?

II. For a drug to be approved for the treatment of hyperuricemia associated with gout, what additional information besides uric acid levels are important to collect?

- Please discuss the clinical endpoints of a reduced number of gout attacks and decreased size of tophi in trials of uric acid lowering drugs.
- Are there preferred methods for measuring tophi (i.e. exam or imaging)?
- Is there more value in evaluating either the absolute number of gout attacks or the relative reduction in number of attacks?

III. Individuals with gout may demonstrate a broad range of uric acid levels.

- Please discuss the range of uric acid levels that would reflect meaningful inclusion or exclusion criteria.
- Are there any advantages to recruiting patients with uric acid in a specified range such as 8-12 mg/dL (representing similar total body load of uric acid)?
- Please discuss whether there a rationale for studying individuals with values of uric acid over 12 mg/dL.
- Is there value in stratifying patients by uric acid level?

IV. Patients with gout may have renal insufficiency.

- Discuss the value of including or excluding such patients in clinical trials.
- If they are to be included, what range of serum creatinine levels would be important to consider for inclusion?

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Questions to the Committee (cont.)

V. Uric acid lowering drugs such as allopurinol are sometimes used at doses higher than those labeled.

- Discuss the utility of studying multiples (such as 2x the highest dose) of the proposed maximum efficacious dose of a new drug.

VI. Please discuss what could be considered an optimal duration for these trials.

VII. Please discuss the implications of placebo vs. active controls and superiority vs. non-inferiority designs for clinical trials of uric acid lowering drugs.

- Is there sufficient data available in the literature to establish a generally accepted response rate for allopurinol that could be used for calculating a non-inferiority margin?

VIII. Please discuss the implications of concomitant therapies.

- Can concomitant drugs such as colchicine or NSAIDs be continued during clinical trials for chronic gout?
- Please discuss the implications of permitting or prohibiting the use of concomitant diuretics or low dose ASA.
- Is there value in recommending or prohibiting a particular diet?
- Is it appropriate to restrict alcohol use?
- Please discuss issues concerning the enrollment of patients with kidney stones.
- Please discuss inclusion of heart/renal transplant patients, especially those on drugs such as cyclosporine?