Questions to the Committee

Phosphate binders
October 16, 2007

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

The Advisory Committee is asked to opine on the basis for approving phosphate binders for the treatment of hyperphosphatemia in patients not yet on dialysis (hereinafter, "pre-dialysis").

All currently approved products have indications for use only in patients on dialysis, although there is no cautionary language about use pre-dialysis. All approved products have indications for reducing serum phosphate level in dialysis patients; none carries a claim for reducing bone disease or ectopic calcifications, improving symptoms, or prolonging life.

The sponsors (Fresenius Medical Care, Genzyme Corp, and Shire Pharmaceuticals) are proposing an extension of the indication to pre-dialysis patients (CKD Stage 4) with no further outcome studies.

The Division does not question whether these drugs are effective in lowering serum phosphate in pre-dialysis patients; they are effective in so doing in patients on dialysis and in normal volunteers. The question is whether there is adequate evidence of net clinical benefit to warrant recommending such use.

Since serum phosphate is not a clinical end point (by which one means death, morbidity, symptoms, or the ability to conduct activities of daily living), the discussion will mostly be about whether there is adequate evidence to conclude that serum phosphate is a validated surrogate for some clinical benefit.

Surrogacy requires the marker to be plausibly part of the pathogenesis of the disease, to have a quantitative association with the clinical outcomes of interest, and to have the relationship to outcomes persist when the marker is affected by a variety of interventions involving a variety of mechanisms.

This last requirement is usually considered to be critical, since there are numerous examples of interventions that affect their targeted biomarkers, but have not led to the desired clinical effects. These examples include torcetrapib affecting HDL, encainide and flecainide affecting VPBs, and inotropes affecting cardiac output.

In the questions that follow, you are first asked whether surrogacy has been established in the setting for which the indication is sought, and then, if not, whether there is an adequate basis for belief that benefits in the dialysis setting lead to incremental benefits when the treatment is applied at an earlier stage of renal disease.

1. One possible theory for approving phosphate binders for use in pre-dialysis patients is the following:

   > Serum phosphate is a valid surrogate for clinical benefit *in pre-dialysis patients*.

   - For what clinical outcomes is serum phosphate plausibly part of the pathogenesis?
   - Considering only the variability related to the natural history of the disease, for which clinical outcomes has serum phosphate been shown to be predictive of risk?
   - For which clinical outcomes have interventions targeting serum phosphate in the pre-dialysis setting been shown to alter risk in the manner predicted by the change in phosphate?
   - **<u>Vote</u>: Is serum phosphate a validated surrogate for clinical outcomes among pre-dialysis patients?**
   - If you voted *yes* above, please say whether you believe the clinical benefits to be manifest before patients require dialysis and why you believe this.

2. A second theory for approving phosphate binders for use in pre-dialysis patients is the following:

   > Serum phosphate is a valid surrogate for clinical benefit *in dialysis patients*, and earlier intervention is beneficial.

   Let us first consider whether serum phosphate is a valid surrogate in dialysis patients.

   - In the previous question, you described where you thought serum phosphate was in the pathophysiological chain to particular clinical end points. Please add anything you think relevant to distinguish pre-dialysis and dialysis settings.
   - For which clinical outcomes have interventions targeting serum phosphate in the dialysis setting been shown to alter risk in the manner predicted by the change in phosphate?
   - **<u>Vote:</u> Is serum phosphate a validated surrogate for clinical outcomes among dialysis patients?**
   - If you voted *no* above, please say whether you believe specific clinical benefits are, nevertheless, attributable to treatment of elevated serum phosphate in dialysis patients, and if so, what the benefits are and why you believe this.

3. If you believe that there is adequate evidence linking changes in serum phosphate to clinical outcomes in dialysis patients, then the issue is when one should initiate such treatment.
    - Please evaluate the following as risks of early treatment with phosphate binders. Please indicate if you believe these risks to be product-specific.
        - Minor gastrointestinal adverse events
        - Major gastrointestinal adverse events
        - Drug interactions
        - Interference with absorption of nutrients
        - Heavy metal accumulation
        - Development of intolerance to phosphate binder products
        - Others?
    - Please describe the incremental benefits of use of phosphate binders in pre-dialysis patients over use in dialysis patients.
    - Please evaluate the incremental benefits of pre-dialysis use compared with the risks.
4. **Vote: Should the indications for phosphate binders extend to use in pre-dialysis patients? Please make any appropriate product-specific qualifications**.
5. If you voted *no* above, please outline what data would provide adequate support to establish a claim for use of phosphate binders in pre-dialysis patients.