King Pharmaceuticals,™ Inc.
Research and Development
4000 CentreGreen Way, Suite 300
Cary, North Carolina 27513

919-653-7042
919-653-7001
Fax: 919-653-7070
charles.pamplin@kingpharm.com

Charles L. Pamplin, III, M.D.
Vice President, Medical Affairs

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Comments Presented to the Cardiovascular and Renal Drug Products Advisory Panel

Good afternoon, I am Dr. Charles Pamplin, Vice President of Medical Affairs, representing King Pharmaceuticals. First of all, we would like to take this opportunity to recognize the FDA for bringing greater awareness to the medical community on the importance of risk reduction. Hypertension is an important public health issue which is too often under treated despite all that is known about its effects and the numerous evidence-based treatment guidelines. We support the use of the product label as a means to link the importance of hypertension treatment with disease outcomes. As noted at the most recent meeting of the American Society of Hypertension, hypertension is a complex cardiovascular disorder. It is not just a collection of elevated blood pressure values, but rather "a progressive cardiovascular syndrome with many causes that result in both functional and structural changes to the heart and vascular system."

We believe that it is important to acknowledge the complexities and limitations of extrapolating benefit between drugs of the same and different classes. Traditionally we have relied on mechanisms of action to determine a drug's class. While this provides a framework to compare and contrast therapeutic agents, it does not imply equality. Clinical studies have often shown differences among drugs with similar mechanisms of action. Significant differences related to bioavailability, distribution, metabolism, clearance and receptor affinity exist both within and between various classes of anti-hypertensives. Of key importance and not to be underestimated, dosage is a critical aspect of achieving benefit. Assigning similar benefits to drugs within a class without a clinical outcomes trial that is powered appropriately and capable of identifying the optimal dose, may expose patients to inferior treatment and unacceptable side effects. Any labeling which includes common information pertaining to the importance of lowering of blood pressure, and the possible benefit on cardiovascular disease, must recognize these differences as matters of both efficacy and safety and allow for clarifying information about what is and is not known about drugs in the class.

Drugs with similar blood pressure lowering effects may have other "non-class effects" which are unrelated to the decrease in blood pressure, but which can have an important impact on clinical endpoints, either positive or negative. Drugs with similar effects on blood pressure do not always have similar effects on outcome. Stroke is the clinical endpoint most closely associated with blood pressure reduction, and yet in randomized trials, such as LIFE, similar blood pressure reduction led to different outcomes in stroke. In the ALLHAT study, treatment with doxazosin, which achieved blood pressure control, was associated with a doubling of heart failure rate.

Altace®, King Pharmaceuticals' branded form of ramipril, is one of the medications with proven clinical cardiovascular endpoint data that is widely interpreted to support risk reduction beyond that expected by blood pressure reduction alone. While blood pressure reduction in the HOPE trial was relatively modest by design, the impact of ramipril on the composite endpoint of reduction of cardiovascular death, myocardial infarction or stroke far exceeded the expectations of the study investigators. Utilizing independent observational analyses from other studies and that derived jointly from the World Health Organization / International Society of Hypertension (WHO/ISH), the relative risk reduction in myocardial infarction and stroke was significantly greater than estimates based on actual achieved reduction in blood pressure in this study. Furthermore, outcomes data from HOPE indicate a similar risk reduction benefit in patients who either were normotensive or were controlled hypertensives. Therefore, while ramipril does reduce blood pressure, the majority of its benefit on cardiovascular risk reduction cannot be attributed solely to an anti-hypertensive effect. And thus, to extrapolate its cardiovascular morbidity and mortality benefits to other agents solely on the basis of the reduction in blood pressure may be inappropriate.

I want to emphasize that hypertension is an important public health issue. We should as a medical community, do everything possible to improve its detection and adequate treatment. We support labeling that would recognize the importance of this syndrome. However, the differences between classes are real and significant, and in the interest of appropriate medical treatment, these should not be ignored. While the differences in molecular structure within a class may appear subtle, the consequences of those differences are far from subtle. Evidence based practice paradigms and individual patient needs must be taken into account when choosing an anti-hypertensive agent to maximize reduction in cardiovascular morbidity and mortality. Optimizing risk reduction would be best achieved by identifying a patient's co-morbidities and utilizing agents with proven effective outcomes data.