Guidance for Industry

Labeling for Outcome Claims for Drugs to Treat Hypertension

DRAFT GUIDANCE

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For questions regarding this draft document contact (CDER) Mr. Devi Kozeli 301-796-1128.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

Spring 2006
Labeling

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I. INTRODUCTION

This guidance is intended to assist applicants in developing labeling for outcome claims for drugs that are indicated to treat hypertension. In this context, "drug" includes manufactured or biologically derived, pharmacologically active agents.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but it is not required.

II. BACKGROUND

With few exceptions, labeling for antihypertensive drug products says that they are indicated to reduce blood pressure, but the labeling is mute on the clinical benefits expected from blood pressure reduction. Blood pressure control is, however, very well established as beneficial, and inadequate treatment of hypertension is acknowledged as a significant public health problem. The Agency believes that, by making the connection between lower blood pressure and improved outcomes more explicit in labeling, it can encourage appropriate use of these drugs. On June 15, 2005, the Cardio-Renal Advisory Committee met in open public session to discuss class labeling for outcome claims for drugs that are indicated to treat hypertension[2]. The Committee voiced a broad consensus in favor of labeling changes to describe briefly the clinical benefits expected of all antihypertensive drugs. The labeling proposed in this guidance is consistent with the recommendations of the Advisory Committee. This draft guidance is being made available to afford the public the opportunity to comment on both the intent of the labeling

[1] This guidance has been prepared by the Division of Cardiovascular and Renal Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] Links to meeting materials, including a transcript, can be found at http://www.fda.gov/ohrms/dockets/ac/cder05.html#cardiovascularRenal.

revisions and the specific proposed language. The intent of the guidance is to provide common labeling for antihypertensive drugs except where differences are clearly supported by clinical data. After publication of a subsequent final guidance, sponsors will be encouraged to submit labeling supplements containing the new language.

III. DISCUSSION

Actuarial data and later epidemiological studies such as the Framingham Heart Study have shown that elevations in blood pressure (systolic or diastolic) are associated with an increased risk of cardiovascular events. These data show that this relationship is monotonic—the higher the blood pressure, the higher the absolute risk—and non-linear—the higher the blood pressure, the steeper the absolute risk increase per mmHg.

Placebo-controlled outcome studies have been conducted with drugs in numerous pharmacological classes (diuretics, beta-adrenergic receptor blockers, direct vasodilators, and calcium channel blockers), and large studies consistently have found reductions in the risk of cardiovascular events. The clearest effect has been reduction in the risk of stroke, but there have also commonly been reductions in the risk of myocardial infarction and cardiovascular mortality. Positively controlled studies with more recently developed drug classes, ACE inhibitors and angiotensin receptor antagonists, appear to share these clinical benefits. The decrease in blood pressure is very likely to be responsible for these benefits, because the outcome studies involved a wide variety of drug classes, sharing few properties other than the effect on blood pressure. The outcome studies all involved treatment regimens using more than one agent to control blood pressure, so the data cannot unequivocally distinguish the contributions of individual drugs or classes.

Numerous single studies (e.g., ALLHAT) and pooled analyses have tested whether drugs given to achieve the same blood pressure goals have the same clinical benefits. To date, such studies have not distinguished the effects of different treatments on the major hypertension-related outcomes (strokes, myocardial infarction, and cardiovascular mortality). Individual drugs—and perhaps drug classes—may have differences in effects on various other end points, presumably because of pharmacological effects other than blood pressure reduction. These other properties of antihypertensive drugs (e.g., effects on heart failure or diabetic nephropathy) will often be a reasonable basis for deciding which drugs to use or to use first.

Although the effects of lowering blood pressure appear to apply generally to antihypertensive drugs, the fact that some drugs (or drug classes) have specific information is also of interest, and such data should be reflected in the Clinical Trials section of labeling for those products. Placebo-controlled trials would be informative, and positive-controlled data demonstrating a superior outcome are also clearly interpretable. Positive-control data distinguishing no outcome differences, such as from ALLHAT, may also be included in labeling, if the drug's effect can be interpreted as adequately similar to that of a valid reference drug. While belonging to the same class as agents with proven outcome benefits is thought to be good, labeling does not usually include descriptions of another drug's trials.

Blood pressure is one of numerous risk factors for cardiovascular disease, and disease management should address all risk factors. Most outcome trials in hypertension preceded current lipid-lowering therapy or wide use of aspirin, so formal measures of their interaction are unavailable. It is clear, however, that these other therapies are effective in patients who are and who are not receiving antihypertensive therapy.

Patients whose risk for cardiovascular events is high for reasons other than blood pressure, particularly patients with diabetes mellitus, receive a disproportionately larger absolute risk reduction per mmHg of blood pressure reduction than do patients without such additional risk factors. Therefore, the treatment goal for blood pressure should be lower in such high-risk patients.

IV. RECOMMENDATIONS FOR LABELING

The following text should be inserted at the beginning of the **Clinical Trials** section or under **Clinical Trials; Hypertension**, as appropriate:

> High systolic or diastolic pressure causes increased cardiovascular risk and the risk increase per mmHg is greater at higher blood pressures. Numerous drugs from a variety of pharmacologic classes, whose only common property is to reduce blood pressure, have been shown to reduce cardiovascular morbidity and mortality, and it can be concluded that the blood pressure reduction is responsible for those benefits. The largest and most consistent outcome benefit has been a reduction in the risk of stroke, but reductions in myocardial infarction and cardiovascular mortality have also often been seen.
>
> Some antihypertensive agents have smaller blood pressure effects (as monotherapy) in blacks, and many antihypertensive agents have additional effects—on angina, heart failure, or diabetic kidney disease, for example—and these considerations may guide selection of therapy. Many patients will require more than one drug to achieve blood pressure goals, but the cardiovascular risks increase steeply with increased blood pressure, so that even modest reductions of severe hypertension can provide substantial benefit. Relative risk reduction from blood pressure reduction is similar across populations with varying absolute risk, so the absolute benefit is greater in patients, like diabetics, at higher risk independent of their hypertension, and such patients will benefit from more aggressive treatment to a lower blood pressure goal. Control of blood pressure should be part of comprehensive cardiovascular risk management, including lipid control, diabetes management, appropriate use of aspirin, smoking cessation, and exercise. For specific advice on goals and management, see published guidelines, such as those of the National High Blood Pressure Education Program's Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC).

Following these introductory paragraphs, the label can have a summary of placebo- or active-controlled trials showing the specific drug's outcome benefits in hypertension. If there are no such data to cite, one of the following two paragraphs must appear:

> There are no studies of DRUGNAME or members of the DRUGCLASS demonstrating reductions in cardiovascular risk in patients with hypertension.

or

> There are no studies of DRUGNAME demonstrating reductions in cardiovascular risk in patients with hypertension, but at least one pharmacologically similar drug has demonstrated such benefits.

In the latter case, the sponsor's application would need to describe the other drugs' studies supporting the claim, but the trial descriptions would not appear in labeling.

Text modeled after the following paragraph should be substituted for a drug's indication in hypertension.

> DRUGNAME is indicated for the treatment of hypertension, to reduce the risk of cardiovascular events, primarily fatal and non-fatal strokes and myocardial infarctions. These benefits have been seen in controlled trials of antihypertensive drugs from a wide variety of pharmacological classes { including this drug | including the class to which this drug principally belongs } . { There are no controlled trials demonstrating risk reduction with DRUGNAME. }

Extra language, such as "DRUGNAME may be used alone or in combination…," can be retained.