Guidance for Industry

Hypertension Indication: Drug Labeling for Cardiovascular Outcome Claims

DRAFT GUIDANCE

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

March 2008
Labeling

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Guidance for Industry[1]
Hypertension Indication: Drug Labeling for Cardiovascular Outcome Claims

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I. INTRODUCTION

This guidance is intended to assist applicants in developing labeling for cardiovascular outcome claims for drugs[2] that are indicated to treat hypertension. With few exceptions, current labeling for antihypertensive drug products includes only the information that these drugs are indicated to reduce blood pressure; the labeling does not include information on the clinical benefits related to cardiovascular outcomes expected from such blood pressure reduction. However, blood pressure control is well established as beneficial in preventing serious cardiovascular events, and inadequate treatment of hypertension is acknowledged as a significant public health problem. The Food and Drug Administration (FDA) believes that the appropriate use of these drugs can be encouraged by making the connection between lower blood pressure and improved cardiovascular outcomes more explicit in labeling. This guidance is intended to recommend standard labeling for antihypertensive drugs except where differences are clearly supported by clinical data. After this guidance has been finalized, applicants will be encouraged to submit labeling supplements containing the new language.

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 not required.

[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] For the purposes of this guidance, *drug* includes drugs regulated under section 505 of the Federal Food, Drug, and Cosmetic Act and biological products regulated under section 351 of the Public Health Service Act.

II. BACKGROUND

On June 15, 2005, the Cardiovascular and Renal Drugs Advisory Committee met in open public session to discuss class labeling for cardiovascular outcome claims for drugs that are indicated to treat hypertension.[3] The committee voiced a broad consensus in favor of labeling changes to describe briefly the clinical benefits related to cardiovascular outcome expected from lowering blood pressure with any antihypertensive drug. The labeling proposed in this guidance is consistent with the advisory committee's recommendations.

III. JUSTIFICATION FOR ADDING OUTCOME CLAIMS TO LABELING

Actuarial data and 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 nonlinear, approximately exponential — the higher the blood pressure, the greater the absolute risk increase per mmHg. Systolic pressure may be more important than diastolic pressure, especially in the elderly.

The effect of blood pressure on relative risk appears to be similar in people at high or low absolute risk. Therefore, absolute risk increase per mmHg of blood pressure elevation is much greater in patients whose risk for cardiovascular events is high for reasons other than blood pressure, such as patients with diabetes mellitus, chronic kidney disease, a history of stroke, or cardiovascular disease.

Among adults, placebo-controlled outcome studies have been conducted with combination regimens of drugs in numerous pharmacologic classes (diuretics, reserpine, beta-adrenergic receptor blockers, direct vasodilators, and calcium channel blockers), and large studies have consistently found reductions in the risk of cardiovascular events. The largest effect has been reduction in the risk of stroke, but reductions in the risk of myocardial infarction and cardiovascular mortality also have been seen. Positive- (or active-)[4] controlled studies with drugs from more recently developed classes (angiotensin converting enzyme inhibitors and angiotensin receptor antagonists) indicate that these drugs share these clinical benefits. The similar effects with multiple drug classes with disparate mechanisms of action indicate that it is the decrease in blood pressure, rather than any other property of the drugs, that is largely responsible for these benefits. Because the relative risk from a given blood pressure reduction is the same in people otherwise at high or low absolute cardiovascular risk, the commonly recommended blood pressure goals are lower in patients at high cardiovascular risk (e.g., diabetes mellitus, lipid abnormalities).

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

[4] See 21 CFR 314.126(b)(2)(iv).

The outcome studies have all involved treatment regimens with more than one drug to achieve the goal blood pressure, so the data cannot easily be used to distinguish the contributions of individual drugs or classes. Numerous meta-analyses and a few large studies (e.g., ALLHAT)[5] have found no consistent differences by class in effects on survival, myocardial infarction, or stroke for regimens achieving the same blood pressure goals, but some differences may exist. In addition, individual drugs, and perhaps drug classes, may have differences in effects on other important endpoints, 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) often will be a reasonable basis for deciding which drugs to use or which drugs to use first.

There is no regulatory precedent for extending an outcome claim across a set of pharmacologically distinct drug classes. In this case, however, there have been consistently favorable effects on outcomes across many drug classes. This situation has led us to conclude that the general, qualitative claim of cardiovascular outcome benefits pertains to all classes of antihypertensive drugs.

Although the effects of lowering blood pressure appear to apply generally to antihypertensive drugs, the fact that some drugs (or drug classes) have been studied for specific outcomes also is of interest, and such data should be reflected in the Clinical Trials section of labeling for those drugs. Placebo-controlled trials and positive-controlled trials demonstrating a superior outcome are clearly interpretable. Positive-controlled trials showing no differences on major outcomes, such as from ALLHAT or other studies of substantial size, also can be included in labeling, if the drug's effect can be interpreted as reasonably similar to that of the control drug.

Blood pressure is one of numerous risk factors for cardiovascular disease, and disease management should address all risk factors. Most placebo-controlled 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 reducing cardiovascular events whether or not a patient is receiving antihypertensive therapy.

The clinical benefit of treating hypertension is not well established in pediatric populations.

IV. LABELING RECOMMENDATIONS

A. Highlights

The Indications and Usage section of Highlights should conform in style to other labeled indications, if any, but both hemodynamic and cardiovascular outcomes should be cited. For example:

[5] See JAMA 2002; 288(23): 2998-3007.

DRUGNAME is a [name of class] indicated for the treatment of hypertension. DRUGNAME reduces blood pressure and thereby reduces the risks of stroke and myocardial infarction.

In addition, any important limitations of use should be listed in this section.

B. Full Prescribing Information — Indications and Usage

The Indications and Usage section of the Full Prescribing Information should be modeled after the following paragraph and should be substituted for a drug's indication in hypertension. Optional language and language specific to a drug are shown in braces.

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

Control of high 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).

Elevated systolic or diastolic pressure causes increased cardiovascular risk, and the absolute risk increase per mmHg is greater at higher blood pressures. Numerous antihypertensive drugs, from a variety of pharmacologic classes and having different mechanisms of action, have been shown to reduce cardiovascular morbidity and mortality, and it can be concluded that it is blood pressure reduction, and not some other pharmacologic mechanism, that is largely responsible for those benefits. The largest and most consistent cardiovascular outcome benefit has been a reduction in the risk of stroke, but reductions in myocardial infarction and cardiovascular mortality also have been seen regularly.

Absolute 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, such as diabetics, who are at higher risk independent of their hypertension, and such patients would be expected to benefit from more aggressive treatment to a lower blood pressure goal. Many patients will require more than one drug to achieve blood pressure goals.

Some antihypertensive drugs have smaller blood pressure effects (as monotherapy) in black patients and many antihypertensive drugs have additional effects (e.g., on angina,

heart failure, or diabetic kidney disease), and these considerations may guide selection of therapy.

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

C. Full Prescribing Information — Clinical Studies

The Clinical Studies section of the label should include a summary of placebo- or active-controlled trials showing evidence of the specific drug's effectiveness in lowering blood pressure. If studies demonstrating cardiovascular outcome benefits exist, those studies also should be summarized in this section. If there are no cardiovascular outcome data to cite, one of the following two paragraphs should 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 applicant's application should describe the studies of the other drugs that support the statement, but the trial descriptions should not appear in labeling.

V. DRUG CLASSIFICATIONS FOR ANTIHYPERTENSIVE DRUGS

Table 1 lists, by pharmacologic class, examples of drugs approved for chronic treatment of hypertension. The drugs shown in bold type have specific outcome data in either placebo-controlled or active-controlled as either primary or secondary treatment. For a complete list of approved drugs for chronic treatment of hypertension, contact the Division of Cardiovascular and Renal Products.

203 **Table 1: Examples of Drugs Approved for Chronic Treatment of Hypertension**

Pharmacologic Class	Approved Drugs
aldosterone antagonists	eplerenone, **spironolactone**
alpha adrenergic blockers	**doxazosin**, phenoxybenzamine, phentolamine, **prazosin**, terazosin
angiotensin converting enzyme inhibitors	benazepril, **captopril**, **enalapril**, fosinopril, **lisinopril**, moexipril, perindopril, quinapril, **ramipril**, trandolapril
angiotensin II receptor blockers	**candesartan**, eprosartan, **irbesartan**, **losartan**, olmesartan, telmisartan, valsartan
arteriolar vasodilators	**hydralazine, minoxidil**
autonomic ganglionic vasodilators	mecamylamine
beta adrenergic blockers	**acebutolol**, **atenolol**, betaxolol, bisoprolol, **carvedilol**, carteolol, esmolol, labetolol, **metoprolol**, nadolol, penbuterol, **pindolol**, **propranolol**, timolol
catecholamine-depleting sympatholytics	deserpidine, **reserpine**
central alpha-2 adrenergic agonists	**clonidine**, guanabenz, guanfacine, **methyldopa**
calcium channel blockers	**diltiazem**, **verapamil**
dihydropyridine calcium channel blockers	**amlodipine**, **felodipine**, **isradipine**, **nicardipine**, **nifedipine**, **nisoldipine**
loop diuretics	bumetanide, ethacrynic acid, **furosemide**, torsemide
potassium-sparing diuretics	**amiloride**, triamterene
renin inhibitors	aliskiren
thiazide diuretics	chlorothiazide, **hydrochlorothiazide**, hydroflumethiazide, methyclothiazide, polythiazide
thiazide-like diuretics	**chlorthalidone**, indapamide, metolazone

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