Guidance for Industry

Hypertension Indication: Drug Labeling for Cardiovascular Outcome Claims

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

March 2011
Labeling

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I. INTRODUCTION

This guidance is intended to assist applicants in developing labeling for cardiovascular outcome claims for drugs that are indicated to treat hypertension.[2] With few exceptions, current labeling for antihypertensive drugs 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 recommends standard labeling for antihypertensive drugs except where differences in labeling are supported by clinical data. We encourage applicants 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 advisory 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 — absolute risk increases progressively with increasing blood pressure — and approximately exponential — the absolute risk increase per mmHg increases with increasing blood pressure. 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, the 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 trials have been conducted with combination regimens of drugs in numerous pharmacologic classes (e.g., diuretics, reserpine, beta-adrenergic receptor blockers, direct vasodilators, and calcium channel blockers), and large trials 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.

It is no longer ethical to conduct outcome trials that leave one group with untreated hypertension. Positive- (or active-)[4] controlled trials with antihypertensive drugs from more recently developed classes (e.g., angiotensin converting enzyme inhibitors and angiotensin receptor antagonists) indicate that these drugs share these cardiovascular clinical benefits (although whether these benefits are identical across drugs or drug classes is bound to be less clear). 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

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

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

commonly recommended blood pressure goals are for a lower target blood pressure in patients at high cardiovascular risk (e.g., diabetes mellitus, lipid abnormalities).

The outcome trials have all involved treatment regimens using 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 trials (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 with different mechanisms of action. This observation 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 to antihypertensive drugs generally, 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 STUDIES section of labeling for those drugs. Placebo-controlled trials and positive-controlled trials demonstrating a superior outcome are interpretable. Positive-controlled trials showing no differences on major outcomes, such as from ALLHAT or other trials of substantial size, also can be included in labeling if the drug's effect can be interpreted as reasonably similar to that of the established 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 interactions 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.

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

IV. LABELING RECOMMENDATIONS

A. Highlights

The INDICATIONS AND USAGE section of Highlights, as it pertains to treatment of hypertension, should read as follows:

> DRUGNAME is a [name of pharmacologic class] indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.

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. Optional language and language specific to a drug are shown in braces.

> DRUGNAME is indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure 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, as appropriate, lipid control, diabetes management, antithrombotic therapy, smoking cessation, exercise, and limited sodium intake. Many patients will require more than one drug to achieve blood pressure goals. 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).
>
> Numerous antihypertensive drugs, from a variety of pharmacologic classes and with different mechanisms of action, have been shown in randomized controlled trials to reduce cardiovascular morbidity and mortality, and it can be concluded that it is blood pressure reduction, and not some other pharmacologic property of the drugs, 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.
>
> Elevated systolic or diastolic pressure causes increased cardiovascular risk, and the absolute risk increase per mmHg is greater at higher blood pressures, 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 who are at higher risk independent of their hypertension (for example, patients with diabetes or hyperlipidemia), and such patients would be expected to benefit from more aggressive treatment to a lower blood pressure goal.
>
> Some antihypertensive drugs have smaller blood pressure effects (as monotherapy) in black patients, and many antihypertensive drugs have additional approved indications and effects (e.g., on angina, heart failure, or diabetic kidney disease). 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 Full Prescribing Information should include a summary of placebo- or active-controlled trials showing evidence of the specific drug's effectiveness in lowering blood pressure. If trials demonstrating cardiovascular outcome benefits exist, those trials also should be summarized in this section. See Table 1 in section V for the specific drugs for which the FDA has concluded that such trials exist. If there are no cardiovascular outcome data to cite, one of the following two paragraphs should appear:

> There are no trials of DRUGNAME or members of the [name of pharmacologic class] pharmacologic class demonstrating reductions in cardiovascular risk in patients with hypertension.

or

> There are no trials 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 submission generally should refer to Table 1 in section V. If the applicant believes that Table 1 is incomplete, it should submit the clinical evidence for the additional information to Docket No. FDA-2008-D-0150. The labeling submission should reference the submission to the docket. The trial descriptions should not appear in labeling.

V. DRUG CLASSIFICATIONS FOR ANTIHYPERTENSIVE DRUGS

Table 1 lists, by pharmacologic class, approved drugs for chronic treatment of hypertension. The drugs shown in bold type have specific outcome data in either placebo-controlled or active-controlled trials as either primary or secondary treatment.

Table 1. Approved Drugs 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**
non-dihydropyridine calcium channel blockers	**diltiazem**, **verapamil**
dihydropyridine calcium channel blockers	**amlodipine**, **felodipine**, **isradipine**, **nicardipine**, **nifedipine**, **nisoldipine**
loop diuretics	bumetanide, ethacrynic acid, **furosemide**, torsemide
renin inhibitors	aliskiren
thiazide diuretics	chlorothiazide, **hydrochlorothiazide**, hydroflumethiazide, methyclothiazide, polythiazide
thiazide-like diuretics	**chlorthalidone**, indapamide, metolazone

VI. CARDIOVASCULAR OUTCOME CLAIM CONSIDERATIONS

A. Applicability of User Fees to Cardiovascular Outcome Claim Supplements

We anticipate that few cardiovascular outcome claim supplements will require the payment of user fees because they will not need clinical data for approval.[6]

[6] The definition of *clinical data* for user fee purposes is provided in the guidance for industry *Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees*. The guidance is available on the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. Contact CDER's User Fee Staff for questions concerning the definition of clinical data for user fee purposes.

For example, if applicants follow the recommended language in section IV.B. without additional changes that are supported by clinical data, then we would ***not*** normally anticipate assessment of a user fee. In addition, if applicants follow the recommended language in section IV.C. that states that no cardiovascular outcome data are available, again, without additional changes that are supported by clinical data, we would ***not*** normally anticipate assessment of a user fee. However, if applicants provide for changes to the labeling that need clinical data for approval (e.g., summary of controlled trials showing evidence of the specific drug's effectiveness in lowering blood pressure), then we would normally anticipate a fee.

As noted in section IV.C., an applicant can submit clinical evidence on cardiovascular outcome data to Docket No. FDA-2008-D-150 and include a reference to the docket submission in the labeling submission. This guidance will be revised to include any new labeling changes supported by clinical data submitted to the docket. We anticipate that labeling changes supported by evidence submitted to the docket would not normally be assessed a user fee.

Applicants should contact the appropriate FDA project manager if there is a question about a specific submission. The review division will determine whether approval for a specific cardiovascular outcome claim supplement needs clinical data for approval.

B. Format of Cardiovascular Outcome Claim Supplements

The following information should be included in a prior approval supplement in the order shown:[7]

1. A statement that the submission is a cardiovascular outcome claim supplement, with reference to this guidance and related Docket No. FDA-2008-D-0150
2. Applicable FDA forms (e.g., 356h, 3397)
3. Detailed Table of Contents
4. Revised labeling:
    a. Include draft revised labeling conforming to the requirements in 21 CFR 201.56 and 201.57
    b. Include marked-up copy of the latest approved labeling, showing all additions and deletions, with annotations of where supporting data (if applicable) are located in the submission

To avoid the imposition of fees, other labeling changes (e.g., the addition of adverse event data) should be minimized and provided in separate supplements. However, the revision of labeling to conform to 21 CFR 201.56 and 201.57 may require substantial revision to the ADVERSE REACTIONS or other labeling sections. This is not anticipated to result in a user fee.

[7] See 21 CFR 314.50.

C. Applicability of Cardiovascular Outcome Claims in Promotional Materials

Applicants are encouraged to cite the outcome claims in promotional materials. Although reproduction of the entire INDICATIONS AND USAGE section is encouraged, the minimum description that is recommended is as follows:

> DRUGNAME reduces blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. Control of high blood pressure should be part of comprehensive cardiovascular risk management, including, as appropriate, lipid control, diabetes management, antithrombotic therapy, smoking cessation, exercise, and limited sodium intake. Many patients will require more than one drug to achieve blood pressure goals.

VII. PAPERWORK REDUCTION ACT OF 1995

This guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520).

The time required to complete the information collection for a submission to Docket No. FDA-2008-D-0150 is estimated to average 10 hours per response, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. The time required to complete the information collection for a cardiovascular outcome claim supplement submission is estimated to average 20 hours per response, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. Send comments regarding this burden estimate or suggestions for reducing this burden to:

Food and Drug Administration, Center for Drug Evaluation and Research, Division of Cardiovascular and Renal Products, Attention: Document Control Room, 5901-B Ammendale Road, Beltsville, MD 20705.

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. The OMB control number for this information collection is 0910-0670 (expires 12/31/2022 (Note: Expiration date updated 01/30/2020)).

REFERENCES

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