Food and Drug Administration
Center for Drug Evaluation and Research

Hilton Washington DC/North Hotel, Gaithersburg, Maryland

Summary Minutes of the Cardiovascular and Renal Drugs Advisory Committee meeting on April 26, 2006, 8:00 AM – 12:00 PM session.

The committee discussed the agency's draft recommendations for relabeling of antihypertensive drugs for outcome claims, as a follow-up to the committee's meeting on June 15, 2005, where the committee discussed class labeling of antihypertensive drugs based on the proximity of their data to outcome trials.

These summary minutes for the April 26, 2006 meeting of the Cardiovascular and Renal Drugs Advisory Committee were approved on May 3, 2006,

I certify that I attended the April 26, 2006 meeting of the Cardiovascular and Renal Drugs Advisory Committee and that these minutes accurately reflect what transpired.

_____//S//_____
Cathy A. Groupe, R.N., B.S.N.
Executive Secretary

_____//S//_____
Thomas G. Pickering, M.D., D.Phil.
(Acting Committee Chair)

A verbatim transcript will be available in approximately two weeks, sent to the Division and posted on the FDA website at http://www.fda.gov/ohrms/dockets/ac/cder06.html#CardiovascularRenal

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information office.

(8:00 A.M. – 12:00 P.M.)
Issue: The committee discussed the agency's draft recommendations for relabeling of antihypertensive drugs for outcome claims, as a follow-up to the committee's meeting on June 15, 2005, where the committee discussed class labeling of antihypertensive drugs based on the proximity of their data to outcome trials.

Attendance

Cardiovascular and Renal Drugs Advisory Committee Members Present (voting):
David L. DeMets, Ph.D.
Steven D. Findlay, M.P.H.
Frederick J. Kaskel, J.D., Ph.D.
Thomas G. Pickering, M.D., D.Phil. (Acting Chair)
Ronald J. Portman, M.D.
John R. Teerlink, M.D.
Lynn Warner-Stevenson, M.D.

Guest Speakers (non-voting):
Stephen W. MacMahon, B.Sc., Ph.D., M.P.H., F.A.C.C.

Open Public Hearing Speakers:
Merrill Goozner, Center for Science in the Public Interest
William R. Hiatt, M.D.
John M. Flack, M.D.

Cardiovascular and Renal Drugs Advisory Committee Members Absent:
John M. Flack, M.D., M.P.H.
Robert A. Harrington, M.D., F.A.C.C.
William R. Hiatt, M.D.
Michael A. Lincoff, M.D.
John F. Neylan, M.D. (Industry Representative)

FDA Participants:
Robert Temple, M.D.
Norman Stockbridge, M.D., Ph.D.

Executive Secretary:
Cathy A. Groupe, R.N., B.S.N.

****

The Cardiovascular and Renal Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met from 8:00 A.M. to approximately 12:00 P.M on April 26, 2006, at the Hilton Washington DC/North Hotel, Gaithersburg, Maryland. Prior to the meeting, the members and the invited consultants had been provided the background material from the FDA. The meeting was called to order by Thomas G. Pickering, M.D., D.Phil. (Acting Committee Chair); the conflict of interest statement was read into the record by Cathy Groupe, RN, BSN (Executive Secretary). There were approximately 50 persons in attendance. There were three speakers for the Open Public Hearing sessions.

The agenda was as follows:

Call to Order and Introductions	**Thomas G. Pickering, M.D., D.Phil.** Acting Committee Chair Cardiovascular and Renal Drugs Advisory Committee
Conflict of Interest Statement	**LCDR Cathy Groupe, B.S.N.** Executive Secretary Cardiovascular and Renal Drugs Advisory Committee
Introduction and Background	**Norman Stockbridge, M.D., Ph.D.** Director Division of Cardiovascular and Renal Products

	FDA Center for Drug Evaluation and Research
	Open Public Hearing
Guidance for Industry Labeling for Outcome Claims for Drugs to Treat Hypertension (Draft Guidance)	**Committee Discussion**
	Break
	Continuation of Committee Discussion
	Questions to the Committee
	Adjournment

Questions to the Committee:
The Committee is asked to opine on a draft guidance for adding outcome claims to antihypertensive drugs.

1. General considerations
   1.1. It is the general style of such Guidance to describe the set of conclusions, but not provide enough detail about the matters to allow someone to argue. That is, a Guidance is not a scholarly review of a topic. Should it be?
   - *The committee agreed that it should not be a exhaustive scholarly review*

   1.2. Should we be trying to assess the impact of these labeling changes on public health? How might one do that?
   - *The committee was in generally agreement that the impact should be assessed; there was considerable discussion about who, specifically, should lead these efforts*
   - *Information should make information more transparent to consumers/patients*
   - *Once source of important data cited for this initiative was NHANES*
   - *All 'agents that lower blood pressure' statements should be incorporated into marketing/advertising*
   - *There should be clear, comprehensive language for the lay public*
   - *VA prescribing patterns cited as a model*

   1.3. There are some labeling implications for being a member of a pharmacological class with outcome data.
   1.3.1. Is that a good idea?
   The committee agreed that this was a good idea but:
   - *It is important to distinguish who the audience is when making this determination*

   1.3.2. If so, should the Guidance name the pharmacological classes, their members, and whether the outcome data are adequate?
   - *The committee generally that yes, but even if it is not, it should be made publicly available on the worldwide web*
   - *The committee commented that the class should be named but there was uncertainty about how much detail should be included*
   - *Classes cited for inclusion included Ace Inhibitors, ARBs, Calcium Channel Blockers, Beta Blockers and subgroups of Diuretics*
   - *Recommendations were made to include pharmacologic classes that contribute to outcome data and also include pharmacologic classes that lower blood pressure*

- *Clarification made – classes that: have outcome data; belong to a class that has data; and, antihypertensives that do not have data*

2. Please comment on specific sections of the background and discussion as reproduced below.

2.1. "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."

- *The committee was in agreement with this language*

2.2. "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. 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."

- *The committee was in agreement with this language*

2.3. "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."

- *The committee discussed log-linear versus non-linear and the difference between proportional and absolute risk, in terms of increasing blood pressure measurements*
- *There is a bigger risk reduction if your blood pressure is higher*
- *The committee commented that there may be additional language needed about other risks and their effects on absolute risk*
- *The committee also commented that the systolic measurement is more important than the diastolic, specifically in the elderly*

2.4. "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."

- *The committee commented that the language, as written, may downplay the reduction in myocardial infarctions*

2.5. "Positively controlled studies with more recently developed drug classes, ACE inhibitors and angiotensin receptor antagonists, appear to share these clinical benefits."

- *The committee cited that "positively controlled trials with more recently developed drug classes, Ace Inhibitors and ARBs" suggests that these drugs share the same benefit*
- *The committee suggested changing "positively controlled" to "more recent studies"*

2.6. "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 committee recommended adding "and the beneficial effects appear to be more closely related to the fall of blood pressure than the drugs used to achieve it."*
- *The committee also suggested adding "wide variety of drug classes with a disparate mechanism of action".*

2.7. "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."

- *The committee was in agreement with this language*

2.8. "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)."

- *The committee discussed the omission of heart failure from the language and why.*
- *The committee proposed the inclusion of beta blockers although beta blockers may be less effective than other drugs, particularly in preventing stroke.*
- *The committee suggested changing "not distinguished" to "generally not distinguished" as well as added a few more clarifying statements to put the information into context*

2.9. "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."

- *The committee recommended the inclusion of chronic kidney disease into this language, citing that CKD is significant enough that it should be considered.*
- *The suggestion was made to delete "various" and put "other important" endpoints*

2.10. "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."

- *The committee commented that ASCOT-LLA showed importance of lipid-lowering in hypertension; also ALLHAT*
- *The committee suggested language revision of "most outcome trials in hypertension preceded current lipid-lowering therapy or wide use of aspirin, but there is some evidence that lipid-lowering in hypertensive patients reduces cardiovascular events."*

2.11. "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."

- *The committee agreed the, in the statement, as written, contains two separate issues – difference in slope rather than threshold (discussion)*

2.12. What is missing from the background and discussion? Are there additional caveats or principles that should be included?

- *The committee cautioned that a blanket recommendation should not be interpreted that companies without outcome claims should not be encouraged to due studies*

- *The committee commented that there is a need to preserve assurances of safety and efficacy in the language of these labels and that application of the label should not ignore other safety concerns*
- *Comments were made on recommendations for additional safety studies after marketing to address potential safety concerns*
- *The committee recommended statements that inform about pediatric trials in progress, in an effort to provide further incentive for increased pediatric studies.*

(See transcripts for detailed discussion)

3. Please comment on specific sections of the proposed **Clinical Trials** section of labeling as reproduced below.

3.1. "High systolic or diastolic pressure causes increased cardiovascular risk and the risk increase per mmHg is greater at higher blood pressures."

- *The committee questioned whether comments on relative risk of SBP versus DBP increases will be put into the label?*
- *The committee suggested a more holistic assessment of absolute risk rather than a focus on mmHg aspect*
- *The committee recommended adding "for any given risk" statements to the language*

3.2. "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 committee agreed that this statement is repetitive and refers to the statements in 2.9*

3.3. "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."

- *The committee agreed that this statement is repetitive and refers to the statements in 2.9*

3.4. "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."

- *The committee was in general agreement that there needs to be revision to this language, specifically the first part of the sentence*
-

3.5. "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."

- *The committee was unclear about why both statements are included in the same sentence, recommended revision to the language*
- *The committee commented that the intent should not be recommend a particular drug but rather, there are various drugs for various indications; patients may need more than one drug*

3.6. "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."

- *The committee and the Agency agreed that this statement should be moved to 3.1.*

3.7. "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."

- *The committee recommended the addition of additional risk reductions such as weight reduction but otherwise agreed on the language*

3.8. "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)."

- *The committee was in agreement with this language*

3.9. There follows an opportunity to describe outcome trials involving the specific drug being labeled. In the absence of such data, one is supposed to insert one of the following:

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

- *The committee was in agreement with this language*

3.9.2. "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."

- *The committee was in agreement with this language*

3.10. What is missing from the **Clinical Trials** section of labeling? Are there additional caveats or principles that should be included?

- *The committee agreed that the inclusion of the negative effects of hypertension should be strongly emphasized in the language (i.e. hypertension results in stroke, MI, death,…) as introductory statements in the label. This will highlight why hypertension control is important*
- *The committee suggested earmarking differences on drug effects on heart failure and kidney disease*
- *This statement should be followed by statements 3.7, 3.8 and the 3.1.*
- *The committee also suggested distinguishing between populations such as the elderly*

(See transcripts for detailed discussion)

4. Please comment on specific sections of the proposed **Indications** section of labeling as reproduced below.

4.1. "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. }"

- *The committee suggested changes to the first part of the statement as follows: "…treatment of hypertension. Treatment of hypertension reduces the risk of cardiovascular..."*
- *The committee questioned the inclusion of fatal and non-fatal in the language of the first sentence.*

4.2. What is missing from the Indications section of labeling? Are there additional caveats or principles that should be included?

- *The committee reemphasized the need for sufficient safety data, suggesting a safety database in hypertension trials of new drugs.*
- *The committee commented that early drug development discussions should incorporate a request for long-term outcome safety data.*

- *The committee further discussed the need to distinguish between a safety database and the need for long-term trials*
- *The Agency commented that there are current initiatives underway to revise the current Guidance of Antihypertensive drugs.*

(See transcript for detailed discussion)

The committee adjourned at approximately 12:00 P.M.