Hypertension: Conducting Studies of Drugs to Treat Patients on a Background of Multiple Antihypertensive Drugs

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact Stephen Grant at 301-796-2240.

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

July 2018
Clinical/Medical

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TABLE OF CONTENTS

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I. INTRODUCTION

This guidance is intended to clarify the recommended approach for sponsors developing drugs to treat hypertension for patients who are on a background of multiple antihypertensive drugs.

Sponsors have approached FDA to discuss development programs for drugs intended to treat *resistant hypertension*, which sponsors have defined as hypertension not adequately controlled by maximally tolerated doses of three or more antihypertensive drugs with different mechanisms of action. FDA encourages development of additional classes of drugs for hypertension, particularly classes of drugs that demonstrate effects when added to currently available therapies.

In general, FDA's guidance documents 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.

II. BACKGROUND

Elevated blood pressure increases the risk of stroke, cardiovascular death, heart failure, and myocardial infarction. Drugs that lower blood pressure have been shown to reduce these risks significantly.

FDA has approved many drugs to lower blood pressure (antihypertensive drugs). These drugs have a variety of mechanisms of action. Antihypertensive drugs are uniformly labeled for use "alone or in combination with other antihypertensive agents," reflecting the fact that adding an

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

antihypertensive drug to another antihypertensive drug with a different mechanism of action is expected to result in further reduction of blood pressure.

The labeling for antihypertensive drugs does not identify a target blood pressure goal but rather refers prescribers to published guidelines. The target blood pressure goals and the sequence of drugs recommended to get patients to those goals vary among guidelines and have evolved over time as new antihypertensive drugs of various pharmacologic classes have become available since the term *antihypertensive* was first used in the 1970s and as new outcome data have become available.

At present, the most commonly recommended drug classes for initial therapy of hypertension are diuretics, renin-angiotensin system inhibitors, beta blockers, and calcium channel blockers, or a combination of these. Other possible treatments include aldosterone antagonists, alpha blockers, central alpha agonists, and direct vasodilators. Nevertheless, availability of additional antihypertensive drugs with novel mechanisms of action would be valuable.

The term *resistant hypertension* occasionally has been used to describe a patient whose blood pressure is inadequately controlled despite being on three or more antihypertensive drugs. However, the specific term has no clear meaning and does not describe a clear patient subset. As noted, many patients will need two, three, or four antihypertensive drugs to achieve adequate control of blood pressure. Although FDA will not label a drug with a specific claim for *resistant hypertension*, FDA does believe that drugs could be shown to be effective in treating hypertension in patients already on a background of multiple antihypertensive drugs.

III. PATHS TO APPROVAL OF ANTIHYPERTENSIVE DRUGS IN PATIENTS ON A BACKGROUND OF MULTIPLE ANTIHYPERTENSIVE DRUGS

Development in this area is not fundamentally different from standard development of antihypertensive drugs. Sponsors have at least two paths to obtain approval of drugs intended to treat hypertension in patients on a background of multiple antihypertensive drugs:

- Demonstrate superiority to placebo in reducing blood pressure in hypertensive patients on appropriate doses of three or more antihypertensive drugs with different mechanisms of action. This would result in a claim that the new drug is indicated for the treatment of hypertension, to lower blood pressure. The background medications and the range of doses taken during the study, as well as the added effect of the new drug, would be described in the CLINICAL STUDIES section of the resulting labeling.

- Demonstrate superiority to another (or more than one) antihypertensive drug (active comparator) in reducing blood pressure in hypertensive patients already receiving maximum doses of three or more antihypertensive drugs with different mechanisms of action. This would result in a claim that the new drug is superior to the specific active comparator drug for the treatment of hypertension, to lower blood pressure. The active comparator should differ in mechanism of action from the mechanisms of the background medications, and the dose(s) of the active comparator would have to be the maximum

dose. The background medications and the range of doses taken during the study would be described in the CLINICAL STUDIES section of the resulting labeling.