Assessment of Pressor Effects of Drugs
Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Naomi Lowy at 301-796-2240.

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

May 2018
Clinical/Medical

Assessment of Pressor Effects of Drugs

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

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

May 2018
Clinical/Medical

TABLE OF CONTENTS

I. INTRODUCTION 1

II. BACKGROUND 1

III. BLOOD PRESSURE ASSESSMENT: SHORT-TERM USE VS. CHRONIC USE OF A DRUG 4

A. Drugs Intended for Short-Term Use 4

B. Drugs Intended for Chronic Use 4

IV. RECOMMENDED USE OF AMBULATORY BLOOD PRESSURE MONITORING 5

V. STUDY DESIGN ISSUES IN ASSESSING BLOOD PRESSURE EFFECTS FOR DRUGS INTENDED FOR CHRONIC USE 6

A. Control Group 6

B. Study Design 6

VI. REGULATORY CONSIDERATIONS 7

REFERENCES 8

Assessment of Pressor Effects of Drugs
Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to advise sponsors on the premarketing assessment of a drug's effect on blood pressure. Elevated blood pressure is known to increase the risk of stroke, heart attack, and death. The effect of a drug on blood pressure can therefore be an important consideration in benefit-risk assessment.

This guidance is intended to address precision of blood pressure measurements in the assessment of the effects of a drug in development. This guidance recommends systemic characterization of the effect of a drug on blood pressure during drug development.

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

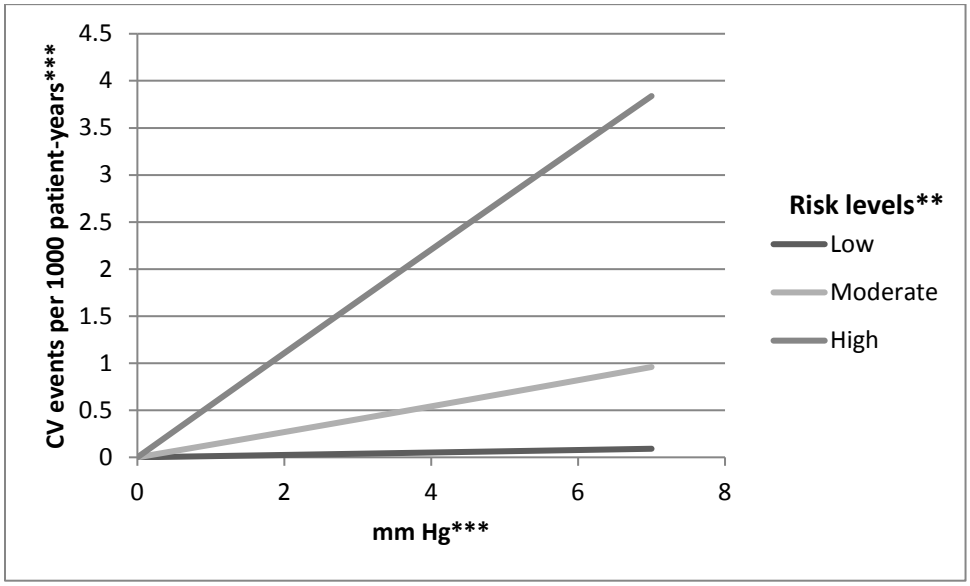
Information from multiple sources indicates that elevated systolic and diastolic blood pressures increase cardiovascular risk. Epidemiologic evidence demonstrates that even a 2- to 3-millimeter of mercury (mm Hg) increase in existing high blood pressure increases rates of stroke, heart attack, and death. MacMahon et al. (1990) evaluated the relationship between diastolic blood pressure and rates of stroke and coronary heart disease (CHD) in nine major, prospective, observational studies. Diastolic blood pressures that were lower by 5, 7.5, and 10 mm Hg were associated with 34 percent, 46 percent, and 56 percent less stroke, respectively, and 21 percent, 29 percent, and 37 percent less CHD. Of note, within the range of diastolic blood pressure studied (70 to 110 mm Hg), the relative reduction in risk associated with a particular decrease in diastolic blood pressure was similar across all levels of diastolic blood pressure, including levels

[1] This guidance has been prepared by the Office of Drug Evaluation I in the Center for Drug Evaluation and Research at the Food and Drug Administration.

that would be considered normal. Comparing the highest risk category of diastolic blood pressure (greater than or equal to110 mm Hg) to the lowest risk category (less than or equal to 79 mm Hg), the risk of stroke was about 10 to 12 times higher; the risk of CHD was about 5 to 6 times higher.

The absolute risk of cardiovascular events is related to multiple risk factors. Data from the Framingham Heart Study have been used to describe the effect of a higher systolic blood pressure (1 to 7 mm Hg) in patients at three risk levels. Figure 1 shows expected increases in cardiovascular events for a chronic elevation in systolic blood pressure in patients whose risks fall within three risk levels (low, moderate, and high).

Figure 1: Relationship of CV Events to Chronic Elevations in Systolic Blood Pressure by Risk Level*



* D'Agostino RB et al., 2008, General Cardiovascular Risk Profile for Use in Primary Care: The Framingham Heart Study, Circulation, 117(6):743–753; data available at Framingham Heart Study Cardiovascular Disease (10-Year Risk) web page at https://www.framinghamheartstudy.org/fhs-risk-functions/cardiovascular-disease-10-year-risk/.
** Low risk = age 25, total cholesterol of 161, high-density lipoprotein (HDL) of 55, untreated systolic blood pressure (SBP) of 125, nonsmoker, nondiabetic.
Moderate risk = age 40, total cholesterol of 205, HDL of 45, untreated SBP of 135, nonsmoker, diabetic.
High risk = age 70, total cholesterol of 225, HDL of 39, treated SBP of 150, nonsmoker, diabetic.
*** CV – cardiovascular; mm HG – millimeter of mercury.

Results from trials show that elevated blood pressure leads to increased cardiovascular events in populations with all levels of risk from other factors, such as elevated low-density lipoprotein (LDL) cholesterol or smoking status. Maintenance of a 5- to 6-mm Hg reduction in diastolic blood pressure with antihypertensive drug regimens typically produces risk reductions of approximately 40 percent in stroke and 15 percent in CHD. Furthermore, the beneficial effect on outcome first occurs within a relatively short period of time, around 6 to 12 months, suggesting that an increased risk from elevated blood pressure would also occur relatively rapidly (Staessen et al. 1997; Veterans Administration Cooperative Study 1970). In the Systolic Hypertension in the Elderly Program (Prevention of Stroke 1991), for example, the reduced rate of stroke is

clearly seen within 1.5 years (and perhaps earlier), and similar findings were seen in the European Working Party on High Blood Pressure in the Elderly trial (Amery et al.1985).

FDA encourages sponsors to seek further discussion to understand the temporal relationship between changes in blood pressure and changes in risk.

This relationship of lower blood pressure to lower rates of stroke and CHD has been observed in outcome studies involving a wide array of antihypertensive drugs, including diuretics, reserpine, hydralazine, beta blockers, calcium channel blockers, and renin angiotensin system inhibitors. The FDA, with the concurrence of the Cardiovascular and Renal Drugs Advisory Committee,[2] considers this relationship to be sufficiently well established leading to the conclusion that all antihypertensive drugs should be labeled with claims that the drugs reduce cardiovascular risk, even if a drug has not been evaluated in cardiovascular outcome studies. This is reflected in the guidance for industry *Hypertension Indication: Drug Labeling for Cardiovascular Outcome Claims*.[3]

Furthermore, some drugs that produce sustained increases in blood pressure (e.g., rofecoxib, sibutramine, torcetrapib) have been associated with adverse cardiovascular effects. It is therefore reasonable to expect that chronic-use drugs that increase blood pressure will increase cardiovascular risk, with the absolute increase in risk related to the baseline risk, the baseline blood pressure, the duration of treatment, and the magnitude of the blood pressure increase. In the Prospective Randomized Evaluation of Celecoxib Integrated Safety Versus Ibuprofen or Naproxen Ambulatory Blood Pressure Measurement (PRECISION-ABPM) trial, ibuprofen was associated with a 3.7-mm Hg increase in ambulatory systolic blood pressure compared to celecoxib and a 1.9-mm HG increase compared to naproxen, leading to an increase in cardiovascular event rates (Ruschitzka et al. 2017). The overall PRECISION trial showed that there were numerically more cardiovascular events in ibuprofen-treated patients, compared with those who received naproxen or celecoxib (Nissen et al. 2016).

FDA encourages sponsors to seek further discussion on whether the results and interpretation of the PRECISION study are relevant in the context of this guidance.

Although nearly every drug development program has some assessment of the effect of a drug on blood pressure, the methods for assessing blood pressure vary. As a result, the precision of blood pressure measurement differs widely, such that small increases in blood pressure that could be relevant for the overall assessment of the risks of a drug may not be reliably detected in some

[2] See the summary minutes of the Cardiovascular and Renal Drugs Advisory Committee meeting for June 15, 2005, available at https://wayback.archive-it.org/7993/20170404055351/https://www.fda.gov/ohrms/dockets/ac/05/minutes/2005-4145M1.pdf.

[3] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

drug development programs. Several factors can influence the importance of an effect on blood pressure, including the seriousness of the condition being treated, the effect of the drug on the condition, the underlying cardiovascular risk in the patient population most likely to use the drug, the availability of other effective therapies that do not raise blood pressure, strategies that can be used to mitigate the blood pressure effects, and the anticipated duration of treatment with the drug.

For a drug that increases blood pressure, subset (and individual) differences in increases in blood pressure response can possibly exist, just as differences among subsets exist in response to blood pressure-lowering treatment. Characterization of such differences is important.

III. BLOOD PRESSURE ASSESSMENT: SHORT-TERM USE VS. CHRONIC USE OF A DRUG

The decision of how blood pressure is assessed during a clinical trial depends on whether a drug is intended for short-term use or chronic use.

A. Drugs Intended for Short-Term Use

There is little concern about a drug indicated for short-term use that has, at most, small effects on blood pressure, because the cardiovascular risk of small short-term elevations in blood pressure is not thought to be significant. FDA's analysis of placebo-controlled hypertension trials of less than 12-week durations (most were shorter) did not find an increased risk of vascular events in the placebo groups (DeFelice et al. 2008). Large blood pressure-increasing effects are of concern, however, even with drugs intended for short-term use. Therefore, in general, careful assessment of blood pressure using cuff sphygmomanometry (cuff blood pressure measurement) during routine study visits should be adequate to assess the blood pressure effect of drugs intended for short-term use.

When use of clinic blood pressure measurements is appropriate, accuracy can be improved by collecting triplicate measurements of sitting blood pressure in all subjects at baseline (predose), at several visits (at least two visits before the end of the trial), at the end of the interdosing interval (trough measurement; predose), and at peak concentration. Measurements should be made at least 1 minute apart using the same arm at each visit.

It is important that measurements be recorded to the nearest even number in mmHg.[4]

B. Drugs Intended for Chronic Use

There is greater concern with the effect of a drug on blood pressure when the drug will be used chronically. As noted above, epidemiologic studies show that risk is related to blood pressure as a continuous function, and that sustained increases in blood pressure correlate with long-term increased risk of cardiovascular adverse events. It follows that even small, sustained increases in blood pressure (2 to 3 mm Hg) chronically would be expected to have such an effect. Thus, detecting such changes is important for drugs intended for chronic use, and for this reason, a

[4] Recommendations are available on proper measurements of blood pressure (see Whelton PK et al. 2017).

sponsor should include a thorough blood pressure assessment, as described in this guidance, for a drug intended for chronic use. As discussed in section IV. Considerations for Ambulatory Blood Pressure Monitoring, FDA recommends use of ABPM for this assessment, as ABPM is capable of detecting small, but potentially relevant, blood pressure effects. ABPM also assesses effects over a 24-hour period, more relevant than a single time point (Pickering 2000).

IV. RECOMMENDED USE OF AMBULATORY BLOOD PRESSURE MONITORING

Several factors influence the ability to detect small changes in blood pressure. First, blood pressure naturally varies throughout the day (diurnal variation) and with meals and activity and changes in response to stress, including the stress of having one's blood pressure measured (*white coat hypertension*). In addition to these true variations in blood pressure, measurement error is associated with use of a cuff blood pressure measurement (e.g., calibration error, improper auscultation, rounding). Given these variations, blood pressure measurement using a small number of cuff sphygmomanometry measurements may not reliably detect small, but potentially relevant, increases in blood pressure (i.e., 2 to 3 mm Hg). Therefore, FDA recommends the use of ABPM as it provides the precision and accuracy needed to detect these smaller changes in blood pressure. ABPM has several advantages over cuff blood pressure measurements including the following:

- ABPM allows the assessment of blood pressure effects over a 24-hour period.
- ABPM allows for a more precise measurement of an individual's blood pressure than can be achieved through the use of cuff blood pressure measurements.
- ABPM devices can be programmed to collect measurements at specified times.
- ABPM is free of potential investigator bias, including tendencies to round up or down.
- ABPM provides a large number of blood pressure measurements throughout the day, providing both a more precise assessment of average change and greater ability to describe individual variation.

FDA also recommends ABPM for any clinical study designed to describe blood pressure effects over 24 hours. These ABPM measurements should be performed in the patient population for which the drug is being developed, either in a targeted study or as part of a larger study already being conducted for other purposes in this population. In light of the precision of ABPM, the number of subjects needed for such clinical studies may not be very large.

V. STUDY DESIGN ISSUES IN ASSESSING BLOOD PRESSURE EFFECTS FOR DRUGS INTENDED FOR CHRONIC USE

A. Control Group

In general, it is desirable to include a placebo group as the control group. ABPM measurements, as noted, are not influenced by observer bias and provide precision. Nevertheless, there can be changes in blood pressure with time that could obscure drug effects, making inclusion of a placebo group desirable.

FDA encourages sponsors to seek further discussion on this issue, including the arguments for and against using a placebo group as the control in ABPM studies.

B. Study Design

The goal of this careful ABPM assessment of blood pressure is to determine whether a drug has a meaningful effect on blood pressure. The protocol should specify whether systolic, diastolic, or mean blood pressure will be evaluated.

In addition to the natural variability in blood pressure during the day, drug concentrations, and therefore a drug's effect on blood pressure, may vary. To assess the overall effect, blood pressure should be measured throughout the day using ABPM and should be done only after the drug has reached steady state. In general, the results should be based on the integrated mean (i.e., area under the curve, a time-weighted average of the blood pressure throughout the day). Results may suggest that blood pressure elevations are related to drug concentration peaks, which could in turn relate to dose and dosing interval.

The study should be carried out in a patient population with characteristics similar to the intended target patient population (i.e., similar demographic and disease-specific characteristics).

If no blood pressure effect is detected by ABPM in early, small studies, subsequent studies (later phase 2, phase 3) can utilize routine cuff blood pressure measurement monitoring, which would detect large effects in specific individuals. Even though early, small studies will not be useful in detecting subgroup effects, an absence of an overall blood pressure effect should provide reassurance that a subset of patients does not have a large blood pressure effect. In this case, routine cuff blood pressure measurements would be sufficient in phase 3 studies.

If the drug increases blood pressure in the overall patient population, the sponsor should obtain additional information about the effects of the drug in relevant subsets of the population with potentially larger effects (e.g., patients with pre-existing hypertension, patients with impaired renal status).

VI. REGULATORY CONSIDERATIONS

Large drug-induced elevations in blood pressure are relevant for all drugs, even for those intended for short-term use. Smaller elevations of blood pressure of even a few mm Hg can also be a concern when the drug is intended for chronic use, particularly when the target population is at increased cardiovascular risk. As noted above, the proportional risk increase for a given blood pressure increase appears to be similar for people with low and high blood pressure, but the increase in absolute risk would be very small for a person at low baseline risk (i.e., age 25, normal LDL and high-density lipoprotein, not diabetic, and normotensive) and becomes progressively greater as the number and severity of risk factors increases, as shown in Figure 1 in section II. Background.

FDA encourages sponsors to seek further discussion on the best regulatory approach to interpret drug's blood pressure effect including asking the following: Is there a specific, identified increase applied across development programs that is cause for concern, or should each development program have its own threshold as it takes risk tolerance into consideration?

The approach outlined in this guidance—identifying drugs that increase blood pressure and determining the size of the effect—should be factored into the overall benefit-risk assessment for the drug, recognizing that increasing blood pressure can be acceptable or can be managed satisfactorily in many circumstances. This assessment should include the consideration of any steps that could be taken to mitigate the risk of increased blood pressure, such as patient selection, pretreatment assessments, blood pressure monitoring in some or all patients, and planned use of blood pressure-lowering treatments.

REFERENCES

Amery A et al., 1985, Mortality and Morbidity Results from the European Working Party on High Blood Pressure in the Elderly Trial, Lancet, 1(8442):1349–1354.

D'Agostino RB et al., 2008, General Cardiovascular Risk Profile for Use in Primary Care: The Framingham Heart Study, Circulation, 117(6):743–753.

DeFelice A et al., 2008, The Risks Associated With Short-Term Placebo-Controlled Antihypertensive Clinical Trials: A Descriptive Meta-Analysis, J Hum Hypertens, 22(10):659–668.

MacMahon S et al., 1990, Blood Pressure, Stroke, and Coronary Heart Disease. Part 1, Prolonged Differences in Blood Pressure: Prospective Observational Studies Corrected for the Regression Dilution Bias, Lancet, 335:765–774.

Nissen SE et al., 2016, Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis, N Engl J Med, 375(26):2519–2529.

Pickering TG, 2000, Ambulatory Blood Pressure Monitoring, Current Hypertension Reports, 2(6): 558–564.

Prevention of Stroke by Antihypertensive Drug Treatment in Older Persons with Isolated Systolic Hypertension: Final Results of the Systolic Hypertension in the Elderly Program (SHEP), 1991, JAMA, 265(24):3255–3264.

Ruschitzka F et al., 2017, Differential Blood Pressure Effects of Ibuprofen, Naproxen, and Celecoxib in Patients with Arthritis: The PRECISION-ABPM (Prospective Randomized Evaluation of Celecoxib Integrated Safety Versus Ibuprofen or Naproxen Ambulatory Blood Pressure Measurement) Trial, Eur Heart, 38(44):3282–3292.

Staessen JA et al., 1997, Randomised Double-Blind Comparison of Placebo and Active Treatment for Older Patients With Isolated Systolic Hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators, Lancet, 350:757–764.

Veterans Administration Cooperative Study Group on Antihypertensive Agents, 1970, Effects of Treatment on Morbidity in Hypertension: II. Results of Patients With Diastolic Blood Pressure Averaging 90 Through 114 mmHG, JAMA, 213(7):1143–1152.

Whelton PK et al., 2017, 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, J Am Coll Cardiol, epub ahead of print November 13, 2017, doi: 10.1016/j.jacc.2017.11.006.