

**Pfizer's Response to ALLHAT: Review of Available
Doxazosin Data on Congestive Heart Failure, Myocardial
Infarction, and Stroke
20 April 2001**

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Executive Summary

The Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) is not a Pfizer trial and is sponsored by the U.S. National Heart, Lung and Blood Institute (NHLBI), a division of the National Institutes of Health (NIH). The doxazosin arm of the trial was discontinued by the sponsor due to (1) a very low probability of demonstrating superior efficacy compared to chlorthalidone for the primary coronary heart disease endpoints and (2) observation of an increased incidence of a secondary endpoint, primarily driven by excess congestive heart failure (CHF) events compared to those taking chlorthalidone, a drug known to be useful in the treatment of CHF. In response to these observations, Pfizer conducted a review of available clinical and postmarketing data on doxazosin, with particular focus on the outcomes of congestive heart failure (CHF), myocardial infarction, and stroke accumulated for more than 13 years of clinical trial and marketing experience. The review of the clinical trial data demonstrates that there is no signal regarding a causal relationship between doxazosin and CHF, myocardial infarction, or stroke in Pfizer's databases. This conclusion is supported by the review of the less rigorous safety database, and by literature review. Although the preliminary results from ALLHAT regarding the relative difference in incidence of CHF between the doxazosin and chlorthalidone groups is strong and persuasive, it does not provide evidence of an adverse effect of doxazosin on cardiac function. Pfizer's clinical experience continues to show that doxazosin remains a safe and effective therapeutic option for hypertension and/or benign prostatic hyperplasia as currently labeled.

ALLHAT

ALLHAT is the first large-scale cardiovascular outcomes trial comparing newer antihypertensive agents (an alpha-blocker, a calcium channel blocker, and an ACE-inhibitor) to diuretic therapy. ALLHAT is not placebo controlled, but rather an active-controlled trial, with the diuretic chlorthalidone serving as the active control. ALLHAT

is sponsored by the National Heart, Lung and Blood Institute (NHLBI), a division of the National Institutes of Health (NIH). Following independent reviews of interim ALLHAT data, the NHLBI discontinued the doxazosin arm due to: 1) a very low probability of superior efficacy for the primary coronary heart disease endpoints (fatal coronary heart disease and nonfatal myocardial infarction) compared to chlorthalidone at the scheduled close of the trial; and 2) a higher rate of one of the secondary endpoints, combined cardiovascular disease events, particularly congestive heart failure, for the doxazosin arm compared to the chlorthalidone arm. There were also observed increases for stroke and angina in the doxazosin group versus the chlorthalidone group that may have been attributable to differences in systolic blood pressure (JAMA, April 19, 2000).

In response to these preliminary ALLHAT results, Pfizer has reviewed data from the following sources: 1) Pfizer-sponsored clinical trials, focusing on the more rigorous data from the double-blind comparative and placebo controlled trials; 2) Pfizer's early alert safety database; and 3) medical literature, looking for any signal of a causal relationship between selected cardiovascular events and doxazosin. Pfizer has also evaluated information regarding ALLHAT that is available in the public domain. Pfizer does not have access to the ALLHAT data because Pfizer is not the study sponsor, and the study is still ongoing with respect to the other agents. Pfizer has requested additional ALLHAT data through the NHLBI.

Review of Pfizer-sponsored clinical trials

The Pfizer-sponsored clinical trials provide the most rigorous database that Pfizer has available for review. These trials were not designed to examine the cardiovascular endpoints of congestive heart failure (CHF), myocardial infarction (MI), or stroke; therefore, the Pfizer sponsored clinical trial data were reviewed from a safety perspective to determine the incidence of adverse event reports of CHF, MI and stroke.

The largest and most rigorous Pfizer database is that including over 47,700 subjects (age 15 to 99) who were identified as receiving doxazosin / doxazosin GITS (maximum total daily dose 0.5 mg to 16 mg) in 271 completed clinical studies for hypertension or benign prostatic hyperplasia (BPH), including the doxazosin GITS MAA submission for hypertension and BPH, as well as the doxazosin NDA submission for BPH. Review of the data from these 271 studies combined indicated a very low incidence ($\leq 0.11\%$) of each of the selected cardiovascular events (CHF, MI and stroke). The incidence of CHF, MI, and stroke events in Pfizer sponsored comparative clinical trials was similar for doxazosin / doxazosin GITS versus pooled comparative agents. A smaller but equally rigorous database is that from the original doxazosin NDA submission for hypertension, review of which provided information consistent with the very low incidence of the selected cardiovascular events. In addition, review of data from ongoing and completed studies without available finalized databases, and therefore considered less rigorous, was undertaken; review of these was also consistent with that from the more rigorous databases. Overall, the review of the clinical trial data from more than 100,000 subjects who received doxazosin / doxazosin GITS, indicate that there is no signal of a causal

relationship between doxazosin / doxazosin GITS and the selected cardiovascular events of CHF, MI, or stroke in Pfizer's databases.

Review of Pfizer Early Alert Safety Database

The Pfizer-sponsored clinical trial database is a rigorous source of data to monitor occurrences of congestive heart failure (CHF), myocardial infarction, and stroke. Although the review of the clinical trial data did not show any signal with regard to these selected cardiovascular events, a review of the early alert safety database was undertaken for CHF or heart failure-like events, myocardial infarction-like events and stroke-like events as supportive evidence.

A search of the Pfizer early alert safety database identified 99 serious clinical study cases reporting cardiovascular events that were thought to be related to doxazosin or doxazosin GITS by the investigator and/or Pfizer. Of these, seven cases involved heart failure-like events, 18 involved stroke-like events, and 13 involved myocardial infarction or related events. Due to multiple events in three cases, there were 34 discrete cases that reported these three types of events. In nearly all of the 34 cases, the patients had at least one concomitant medication or medical history suggestive of pre-existing cardiovascular disorders or other risk factors associated with these events. The treatment indication in all but one of the 34 cases was hypertension. Therefore, these patients appeared to be at high risk of developing heart failure, stroke, myocardial infarction, or related events independent of doxazosin or doxazosin GITS therapy. In addition, based on review of the cases in which the patient was reported to have died regardless of causality, there is no signal indicating that doxazosin or doxazosin GITS therapy places patients at increased risk of death.

A search of the non-clinical-study cases identified a total of 11,359 doxazosin / doxazosin GITS cases, of which there were 190 cases of possible stroke-like events, 154 cases of myocardial infarction-like events and 148 cases of heart failure-like events. To put this number in perspective, it should be noted that during the 13 years that doxazosin has been commercially available when these cases were reported, there have been approximately 4.1 billion patient-days of doxazosin therapy.

The 148 non-clinical study cases reporting heart failure-like events were reviewed. These cases involved 1.3% of all doxazosin/doxazosin GITS cases entered into the database, with a reporting rate of 36 cases/billion patient-days of therapy. The 58 relevant cases of heart failure-like events were further reviewed. The majority of patients was male and elderly, and most had medical histories that appear to have placed the patients at high risk for heart failure-like events independent of doxazosin or doxazosin GITS therapy. In 16 cases the patients were reported to have died, seven of which originated from marketing-based patient compliance programs that involved solicitation of information from consumers. Given that most of the patients were male and elderly, and many were reported to have medical histories that would place them at high risk of heart-failure-like events, there was no signal of a causal relationship with doxazosin or doxazosin GITS.

The 154 non-clinical-study cases reporting myocardial infarction-like events were reviewed. These cases involved 1.4% of all doxazosin/doxazosin GITS cases entered into the database, with a reporting rate of 38 cases/billion patient-days of therapy. There were 128 relevant cases that were further reviewed. This dataset was notable for the nearly 75% of cases originating from marketing-based patient compliance programs. These were reported by consumers and most lacked information regarding concomitant medication and medical history. Most of these patients were male, over 50 years of age, and had risk factors for developing myocardial infarction-like events independent of doxazosin or doxazosin GITS therapy, based on significant medical histories and relevant concomitant therapies. There were 54 patients who were reported to have died, and this outcome did not appear to be associated with doxazosin therapy in these cases. Given that most patients were at risk for myocardial infarction-like events, and the majority of these cases originated from marketing-based patient compliance programs and lacked key information regarding concomitant medication and/or medical history, there was no signal of a causal relationship with doxazosin or doxazosin GITS.

The 190 non-clinical study cases reporting stroke-like events were reviewed. These cases involved 1.7% of all doxazosin/doxazosin GITS cases entered into the database, with a reporting rate of 46 cases/billion patient-days of therapy. Of these, there were 170 relevant cases that were further reviewed. Over half of these cases originated from marketing-based patient compliance programs. Most of these patients were male and elderly. The majority of patients had a medical history or were taking concomitant medication(s) suggestive of concurrent illness that could have predisposed them to stroke or stroke-like events independent of doxazosin or doxazosin GITS therapy. There were 37 patients who were reported to have died, and this outcome did not appear to be associated with doxazosin therapy in these cases. Given that most patients were at risk for these events, there was no signal of a causal relationship with doxazosin or doxazosin GITS.

The number of cases reported to Pfizer that involved heart failure, myocardial infarction and stroke-like events was relatively small compared to all reported cases of adverse events. The characteristics of the patients, as well as their reported medical histories and concomitant medication(s) place them at high risk of experiencing these selected cardiovascular events independent of doxazosin or doxazosin GITS therapy. The number of cases reporting these selected cardiovascular events is small considering more than 4.1 billion patients-days of doxazosin therapy over 13 years of worldwide commercial use. Review of the cases reporting CHF and heart failure-like events, myocardial infarction-like events and stroke-like events supports the conclusion from review of the more rigorous clinical trial data that there is no signal of a causal relationship between these events and doxazosin or doxazosin GITS therapy.

Review of Prescription-Event Monitoring

A Prescription-Event Monitoring (PEM) study of 8,482 patients who had been treated with doxazosin between March 1989 (when doxazosin was first marketed in the United Kingdom) and January 1991 was finalized in January 1995. The rates of events occurring during the first month of treatment were compared with the mean rates recorded during the second to sixth month of treatment. These data were compared with those obtained during PEM studies of seven other drugs also used in the treatment of hypertension and with 'pooled' data. Among the 8,482 patients, the mean age was recorded as 59.3 and the male to female ratio was noted to be 0.8 and where indication was stated, 99% of the patients had received doxazosin for hypertension. The event rates (per 1000 patients) with doxazosin were cardiac failure, 0.5; cerebrovascular accident, 0.2; and ischaemic heart disease, 1.5. The general pattern of these events was consistent with those observed in other PEM studies of antihypertensive agents. The PEM report concluded that "no serious non-fatal events and no deaths were attributed to doxazosin" and they concluded that doxazosin was a safe drug for use in the treatment of hypertension.

Review of Medical Literature

A review of the medical literature was also performed as supportive evidence. As most Pfizer-sponsored clinical trials involving doxazosin / doxazosin GITS were less than 1 year in duration, the literature was reviewed with particular focus on long term data involving the use of doxazosin for one year or greater.

Published long term clinical trials (at least one year in duration) involving treatment with doxazosin and publications (clinical trials or review articles) that included mention of both doxazosin and heart failure in humans were identified. A review of 22 publications revealed that among 5,919 pooled clinical trial subjects, 23 (0.38%) subjects had an adverse event of CHF, 42 (0.71%) had an adverse event of myocardial infarction, and 26 (0.44%) had an adverse event of stroke. Review of the medical literature supports the conclusion of the clinical data review, that there is no safety signal regarding CHF, MI, or stroke in subjects treated with doxazosin for either hypertension or benign prostatic hyperplasia (BPH) in the Pfizer databases.

Conclusion

Review of data from Pfizer-sponsored clinical trials shows that there is no safety signal regarding a causal relationship between doxazosin and CHF, myocardial infarction, or stroke in the Pfizer databases. Review of Pfizer's early alert safety database and of the published medical literature supports the absence of a signal regarding a causal relationship between doxazosin and CHF or heart failure-like events, myocardial infarction or stroke. Based on Pfizer's extensive experience with doxazosin for more than 13 years, both in marketing the product and in the clinical trial program, doxazosin remains a safe and effective therapeutic option for getting patients to goal blood pressure and for treating the symptoms associated with BPH.

Section 1: ALLHAT

The Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) is sponsored by the National Heart, Lung, and Blood Institute (NHLBI), a division of the National Institutes of Health. ALLHAT is a practice-based, randomized, multi-center cardiovascular outcomes trial with two components: an antihypertensive component and a lipid-lowering component. ALLHAT has 625 clinical sites located in the US, Canada, Puerto Rico and the US Virgin Islands. The clinical sites include VA Hospitals, private medicine hospitals, community health centers, health maintenance organizations and specialty practices. In this trial, 42,448 high risk hypertensive patients, 55 years of age or older were randomly assigned to one of four treatment groups. The treatments compared were the diuretic chlorthalidone (active control), the calcium channel-blocker amlodipine, the alpha-blocker doxazosin and the ACE-inhibitor lisinopril. The scheduled follow-up for the study was four to eight years, with an average of six years.

ALLHAT's Data and Safety Monitoring Board (DSMB) is charged with reviewing ongoing safety data. The DSMB meets semi-annually to review cumulative data from the study and to make risk/benefit assessments. One of the DSMB's evaluations was to review the superiority of three of the treatment agents compared to the diuretic chlorthalidone. Due to an inconclusive review by the DSMB, the NHLBI solicited a second independent review, and on January 24th 2000, the NHLBI Director accepted a recommendation to terminate the doxazosin arm. This decision was based on 1) a very low probability of demonstrating superior efficacy for the primary coronary heart disease endpoints compared to chlorthalidone at the scheduled close of the trial; and 2) a higher rate of one of the secondary endpoints, combined cardiovascular disease events, particularly congestive heart failure, for the doxazosin arm compared to the chlorthalidone arm

Consistent with Investigational New Drug (IND) requirements within the US, the NHLBI notified the US Food and Drug Administration (FDA) on February 1, 2000 of its decision. Subsequent to contacting the US FDA, the NHLBI informed the Canadian Therapeutic Products Program (TPP) via phone of its decision.

This decision was conveyed to the ALLHAT Steering Committee on February 3, 2000. The membership of the Steering Committee includes the regional coordinators of the trial and representatives from the clinical trial center (CTC), and the NHLBI. Pfizer has two non-voting representatives on the Steering Committee.

The NHLBI in conjunction with the Steering Committee also notified each ALLHAT investigator of this decision through an investigator letter dated February 16, 2000. Each investigator was provided patient information packets to mail to each patient in the trial.

Release of the preliminary results of ALLHAT was made in a NHLBI press release distributed on March 8, 2000 and at the American College of Cardiology (ACC) meeting held in Anaheim, California, US on March 15, 2000. The ACC also issued a statement

on the preliminary results of the trial on March 15, 2000, with a follow-up clarification on March 23, 2000. A manuscript authored by the ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group entitled “Major cardiovascular events in hypertensive patients randomized to doxazosin versus chlorthalidone” was posted on the website of the Journal of the American Medical Association (website address: www.jama.com) on April 4, 2000, and subsequently published in that journal on April 19, 2000. (The items mentioned above are attached for reference). Further presentations made at the American Society of Hypertension in May 2000 and at the International Society of Hypertension in August 2000 provided no new information.

Study Background

The ALLHAT trial is the first large-scale cardiovascular outcomes trial comparing newer antihypertensive agents (an alpha-blocker, a calcium channel blocker, and an ACE-inhibitor) to diuretic therapy. (The rationale and design of ALLHAT was published in 1996; this publication is appended for reference.) Over 42,000 patients at least 55 years of age, with a history of hypertension (previously documented or on treatment) or newly diagnosed hypertension, and with at least one other cardiovascular disease risk factor, were randomized to receive one of four treatments. The cardiovascular disease risk factors required for participation in the trial included one or more of the following: myocardial infarction or stroke (age indeterminate or occurring at least six months prior to randomization), history of a revascularization procedure, other documented atherosclerotic cardiovascular disease, major ST segment depression or T-wave inversion, Type 2 diabetes mellitus, HDL cholesterol < 35 mg/dL on 2 occasions in the past 5 years, left ventricular hypertrophy by electrocardiogram or echocardiography in the past two years, or current cigarette smoking. In order to maintain blood pressure less than 140/90 mmHg, a step 2 or step 3 antihypertensive agent (atenolol, reserpine, clonidine, hydralazine) could be added to the assigned study drug if necessary. Patients could be on more than one add-on agent. In special cases, investigators could choose to prescribe second line antihypertensive drugs other than those provided by the study. Addition of open label agents in the classes under evaluation was discouraged unless there was a specific indication.

The **primary** endpoint of ALLHAT was the combination of fatal coronary heart disease and non-fatal myocardial infarction.

There were four main **secondary** endpoints:

- 1) all-cause mortality;
- 2) combined coronary heart disease (CHD), including death due to coronary heart disease, nonfatal myocardial infarction, coronary revascularization procedures, and hospitalized angina;
- 3) stroke; and

- 4) combined cardiovascular disease (CVD), consisting of death due to CHD, nonfatal myocardial infarction, stroke, angina, revascularization procedures, congestive heart failure (CHF) and peripheral arterial disease.

Preliminary results of ALLHAT

The results of the preliminary analysis of ALLHAT were limited to the hypertensive component of the trial. Only data with regard to the doxazosin and chlorthalidone treatment groups were described, and those data were limited to data available as of December 1999.

Randomization was completed in January 1998 at year four of the study, with 9,067 patients randomized to the doxazosin group and 15,268 patients randomized to the chlorthalidone group. At baseline, the mean age of patients assigned to the chlorthalidone and doxazosin groups was 67 years. The groups were similar with regard to baseline characteristics, including race, gender, education, blood pressure, percentage treated for hypertension, percentage with atherosclerotic cardiovascular disease, ST-T wave changes, Type 2 diabetes mellitus, cigarette smoking, HDL-cholesterol < 35 mg/dL, LDL-cholesterol, HDL-cholesterol, left ventricular hypertrophy and serum biochemistry. The median follow-up was 3.3 years.

After four years, 501 (3.2%) of the chlorthalidone group and 338 (3.7%) of the doxazosin group were lost to follow up. Of those remaining in the trial, 86% of patients assigned to the chlorthalidone group and 75% of patients assigned to the doxazosin group were actually receiving their assigned study medication.

After four years, 40% of patients assigned to the chlorthalidone group and 47% of patients assigned to the doxazosin group were receiving a step 2 or step 3 antihypertensive agent.

With regard to dose of study drug, at four years, 57% of patients assigned to the chlorthalidone group and actually taking chlorthalidone were on the maximal dose of 25 mg/d, and 61% of patients assigned to the doxazosin group and actually taking doxazosin were on the maximal study dose of 8 mg/d.

The results of the preliminary analysis were based on an “intent-to-treat” approach.

The decision to discontinue the doxazosin arm of ALLHAT was made for two reasons:

- there was no difference from the chlorthalidone group in the primary endpoint of combined fatal coronary heart disease and non-fatal myocardial infarction; based on statistical calculations, a beneficial effect of doxazosin over chlorthalidone at the scheduled trial termination was highly unlikely;

- there was a statistically significantly higher incidence of combined CVD events, in particular CHF, for the doxazosin group compared with the chlorthalidone group.

Among the four main secondary endpoints:

- There was no difference between the two groups in all-cause mortality.
- A trend was reported towards a 10% higher risk of combined coronary heart disease in the doxazosin group (n=775 / 9067; 8.5%) than in the chlorthalidone group (n=1211 / 15268; 7.9%) (p = 0.05).
- A trend was reported towards a 19% higher risk of stroke in the doxazosin group (n=244 / 9067; 2.7%) than in the chlorthalidone group (n=351 / 15268; 2.3%) (p = 0.04).
- There was a 25% higher risk of combined CVD in the doxazosin group than in the chlorthalidone group, largely driven by CHF, which was statistically significant (p<0.001). The risk of CHF was almost doubled in the doxazosin group (8.1%) compared with the chlorthalidone group (4.5%) (p<0.001).

The differences between the two groups with regard to combined CVD and CHF were consistently observed among the subgroups that included patients <65 years and those 65 or older; African Americans and non-African Americans; and patients with and without diabetes.

There were also trends reported towards a 16% higher risk for angina and a 15% higher risk for revascularization in the doxazosin group than in the chlorthalidone group.

Although there was no difference in blood pressure between the two groups at baseline, mean systolic blood pressure after four years was 3 mm Hg higher for patients assigned to the doxazosin group than patients assigned to the chlorthalidone group. Standard deviations were not given and details of mean dose were not provided. Mean diastolic blood pressures were the same for the two groups after four years. Both mean systolic and mean diastolic blood pressures for both groups were below goal.

The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group considered that, based on data from earlier clinical trials [including the Systolic Hypertension in the Elderly Program (SHEP) and the Systolic Hypertension in Europe (Syst-Eur) trial], the 3 mm Hg difference in systolic blood pressure may have accounted for most of the increased incidence of stroke and angina, but may have only partially accounted for the increased incidence of CHF in the doxazosin group.

Confounding Issues

Although the preliminary data from ALLHAT regarding the relative difference in CHF incidence between the doxazosin and chlorthalidone groups is strong and persuasive, it does not provide evidence of an adverse effect of doxazosin on cardiac function.

Based on the fact that there was no placebo group in ALLHAT, the ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group state: *“It is difficult to judge whether in ALLHAT the CHF rate with doxazosin is the same, less or more than would be expected without antihypertensive drug treatment.”* The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group discuss the SHEP trial, which was placebo controlled, in which 4.4% of the placebo group developed CHF over 4.5 years of follow-up, compared with 2.3% in the diuretic group. This ratio is the same as that seen in the doxazosin group (8.13) versus the diuretic group (4.45) in ALLHAT. Moreover, the criteria for CHF diagnosis in ALLHAT were adapted from SHEP.

It is important to note that doxazosin was not used in ALLHAT according to labeled recommendations. Patients were titrated more slowly, with dosage increases at monthly intervals rather than the 2 week intervals recommended in the labeling. In addition, the maximum dose used in the study was 8 mg, rather than the recommended maximum of 16 mg. This may have impacted adversely on blood pressure control in the first 6 months or so of the trial, which may have been of particular importance in vulnerable patients.

One would expect a significant number of the ALLHAT patients, who were elderly and high-risk hypertensives, to develop CHF during the course of the study. (Refer to Study Background section for entry criteria) Because the active control in ALLHAT is a diuretic that is a recognized effective treatment for CHF, it is possible that the emergence of CHF during the conduct of the study is masked in the chlorthalidone group, thereby increasing the observed difference in incidence between the groups. Doxazosin is not indicated for CHF.

Figure 3 of the ALLHAT publication (JAMA, April 19, 2000) (presented as Kaplan-Meier Estimates for Outcomes) shows separation in the event curve for CHF beginning in the first few months of treatment, with greater separation occurring during the first year than is seen thereafter. This early separation might be indicative of events related to discontinuation of prior therapy together with initiation of doxazosin therapy. Discontinuation of prior antihypertensive therapy, which may have included a diuretic and/or ACE-inhibitor, without a washout period, may have played a role in the early emergence of CHF in the doxazosin arm. Data on prior therapy were not provided. In addition, none of the protocol-specified add-on agents (atenolol, clonidine, reserpine, hydralazine) are indicated for the treatment of CHF. Data on open-label add-on agents were not provided.

A large percentage of patients analyzed were not taking their assigned study drug (25% in the doxazosin arm and 14% in the chlorthalidone arm at 4 years). Information is required as to how many events occurred in patients actually on their assigned treatment, how

these events relate to blood pressure control, and how blood pressure control relates to therapy and dose. The “intention-to-treat” analysis in the ALLHAT publication does not provide these details.

The ALLHAT publication discusses the small differences in systolic blood pressure between the two treatment arms, but information was not provided as to mean dosage. Without this information, it is not possible to account for differences in systolic blood pressure control.

Although large trials such as ALLHAT are normally reported as “intention-to-treat” analyses, in this instance, an “on therapy” analysis would probably provide a better understanding of the preliminary findings with regard to safety data for doxazosin.

Additional Data Requested

Pfizer requested additional doxazosin data from NHLBI, specifically:

- distribution of CHF and stroke events by therapy, by year, and by presence or absence of baseline antihypertensive therapy;
- pre-event blood pressure in patients with these events, as well as mean blood pressure in the total group assigned to doxazosin and mean blood pressure in the subgroups on doxazosin alone, doxazosin plus other therapy, other therapy but no doxazosin, and no therapy; and
- details of therapy and dose for patients with CHF and stroke events, as well as for the total group and subgroups defined above.

The NHLBI informed Pfizer that they will provide these data for those patients assigned to doxazosin who are not continuing in the lipid-lowering arm of the study (6874 of 9067 patients). These data will be compared to those for the total group assigned to doxazosin, to confirm that they are representative. NHLBI will not provide comparable information for chlorthalidone.

Conclusion

ALLHAT data are preliminary at this time, and further information is needed before a final conclusion can be drawn.

The following information, which is available in the public domain on ALLHAT, can be found in Appendices 1A-1G:

1. Davis BR, Cutler JA, Gordon D, et al. for the ALLHAT Research Group. Rationale and design of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *American Journal of Hypertension*. 1996; 9: 342-360.
2. NHLBI press release - March 8, 2000
3. Messerli FH. Implications of discontinuation of doxazosin arm of ALLHAT (comm.). *Lancet*. March 11, 2000; 355: 863.
4. ACC press release – March 15, 2000
5. ACC clarification – March 23, 2000
6. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major cardiovascular events in hypertensive patients randomized to doxazosin versus chlorthalidone. *JAMA*, April 19, 2000; 283 (15): 1967 – 1975. posted on the website of the Journal of the American Medical Association (website address: www.jama.com) on April 4, 2000.
7. Lasagna L. Diuretics versus alpha-blockers for treatment of hypertension (ed.). *JAMA*. April 19, 2000; 283 (15): 2013-2014. posted on the website of the Journal of the American Medical Association (website address: www.jama.com) on April 4, 2000.

The following relevant background information can be found in Appendices 1H and 1I:

1. Systolic Hypertension in the Elderly Program (SHEP) is summarized in the following publication: Kostis J, Davis BR, Cutler JA, et al. Prevention of heart failure by antihypertensive drug treatment in older persons with isolated systolic hypertension. *JAMA*. 1997; 278: 212-216
2. The Systolic Hypertension in Europe (Syst-Eur) trial is summarized in the following publication: Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Randomized double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. *Lancet*. 1997; 350: 757-764

Section 2: Review of Pfizer Sponsored Clinical Trials

Section 2 Summary

The Pfizer sponsored clinical trials, unlike ALLHAT, were not designed to examine the cardiovascular endpoints of congestive heart failure (CHF), myocardial infarction (MI), or stroke; therefore, the Pfizer sponsored clinical trial data were reviewed from a safety perspective to determine the incidence of adverse event reports of CHF, MI and stroke to see whether any evidence supporting the ALLHAT preliminary findings could be found in Pfizer's clinical study database.

An integrated review of Pfizer's most rigorous clinical trial data identified more than 47,700 subjects (age 15-99) who received doxazosin / doxazosin GITS (maximum daily dose 0.5 mg to 16 mg) in 271 completed clinical studies for hypertension or BPH, including the doxazosin GITS MAA submission for BPH and hypertension, as well as the doxazosin NDA submission for BPH. Review of the data from these 271 studies combined indicated a very low incidence ($\leq 0.11\%$) of each of the selected cardiovascular events (CHF, MI and stroke) among subjects taking doxazosin. The incidence of CHF, MI, and stroke events in Pfizer sponsored comparative trials was similar for doxazosin / doxazosin GITS versus pooled comparative agents. A smaller but equally rigorous database is that from the original doxazosin NDA submission for hypertension, review of which provided information consistent with the very low incidence of the selected cardiovascular events. In addition, review of data from ongoing and completed studies without available finalized databases, and therefore considered less rigorous, was undertaken; review of these was also consistent with that from the more rigorous databases. Overall, the review of the clinical trial data from more than 100,000 subjects who received doxazosin / doxazosin GITS, indicate that there is no signal of a causal relationship between doxazosin / doxazosin GITS and the selected cardiovascular events of CHF, MI, or stroke in the Pfizer clinical databases.

Methodology

Pfizer's Corporate Clinical Trial Registry was searched to identify Pfizer-sponsored, doxazosin / doxazosin gastrointestinal therapeutic system (GITS) clinical studies. Phase I studies (i.e. studies in healthy volunteers) were excluded from this review. Each clinical study was categorized into three types based on the status and availability of the data:

- 1) Completed studies through 28 February 2001 (including studies referenced in the doxazosin New Drug Application (NDA) for benign prostatic hyperplasia (NDA #20,371) filed to the US Food and Drug Administration (FDA) as well

as the doxazosin GITS studies referenced in the Marketing Authorization Application (MAA) filed to the Medicines Control Agency (MCA))

2) Studies referenced in the NDA for hypertension (NDA #19,688) filed to the US FDA.

3) Other studies

1) Completed studies

For the purposes of this review, completed studies are defined as studies with completed subject participation and with finalized databases (i.e., all quality control procedures completed) and available for this review as of 28 February 2001.

Frequency listings of adverse event preferred terms from the finalized databases, were reviewed to select specific terms to identify subjects that experienced selected cardiovascular adverse events, i.e., myocardial infarction (MI), stroke, and congestive heart failure (CHF). The specific preferred terms that were searched are listed in Appendix 2A. Completed studies were analyzed to determine the incidence of the selected cardiovascular events.

2) Studies referenced in the NDA for hypertension (NDA #19,688) filed to the U.S. FDA

Relevant sections of the original doxazosin NDA submission for hypertension were obtained from Pfizer's Regulatory Library. These sections were reviewed to identify previous analysis results related to the selected cardiovascular events of CHF, MI and stroke.

3) Other studies

"Other" studies include studies with ongoing subject participation; studies with study reports for which databases were not available for review; and studies with completed subject participation, but with databases still undergoing quality control procedures. These studies were considered less rigorous, and were reviewed as supportive evidence.

Multiple data sources that were available as of 15 May 2000 were reviewed in order to investigate information from these studies. The data sources that were reviewed include:

- a) US FDA IND Annual Reports
- b) Databases still undergoing quality control procedures
- c) Local medical review of information from country sponsored clinical studies
- d) Study reports

Results

1) Completed studies

A total of 271 doxazosin clinical studies were identified as of 28 February 2001, including the doxazosin GITS MAA submission for BPH and HTN, as well as the doxazosin US NDA submission for BPH. Of the 271 studies, 187 were non-comparative studies while 84 studies involved use of a comparative agent. Appendix 2B provides a list of all 271 studies and indicates whether the studies were comparative, placebo controlled, BPH or cardiovascular.

A total of 47,790 subjects were treated with doxazosin. The age of the subjects treated with doxazosin ranged from 15 to 99 years; 89% of the subjects were 45 years or older. The maximum total daily dose of doxazosin ranged from 0.5 to 16 mg. Duration of treatment was short compared with ALLHAT; the majority of the patients (approximately 40,000) were treated for between 8 and 26 weeks; approximately a further 5,000 were treated for between 26 and 52 weeks.

In the 84 comparative clinical studies, 5281 subjects received doxazosin and 4493 received either placebo or an active comparative agent. Of the 84 comparative studies, 67 were cardiovascular studies and 17 were BPH/urologic studies. The most rigorous data are from 27 placebo controlled studies, 12 of which were cardiovascular studies and 15 of which were BPH/urologic studies.

Of the 47,790 subjects treated with doxazosin, 31 (0.06%) subjects experienced CHF events, 52 (0.11%) subjects experienced MI events and 51 (0.11%) subjects experienced stroke events. Appendix 2C summarizes the treatment emergent, all causality incidence of selected cardiovascular events, by protocol ID.

Table 1 (below) further summarizes the treatment emergent, all causality incidence of selected cardiovascular events by median duration of treatment for the 271 completed studies (≤ 8 weeks, $> 8 - 26$ weeks, $> 26 - 52$ weeks, > 52 weeks)

Table 1: Treatment Emergent, All Causality Incidence of Selected Cardiovascular Events by Median Duration of Treatment for 271 Completed Studies

Median Treatment Duration	Total # of Subjects on Doxazosin	Total # of Subjects on Pooled Comparators	Doxazosin/Doxasozin GITS			Pooled Comparators		
			Number(%) of Subjects with CHF	Number(%) of Subjects with MI	Number(%) of Subjects with Stroke	Number(%) of Subjects with CHF	Number(%) of Subjects with MI	Number(%) of Subjects with Stroke
≤ 8 weeks	5,135	621	1 (0.02%)	3 (0.06%)	2 (0.04%)	0	0	1 (0.16%)
$> 8 - 26$ weeks	39,380	2,422	19 (0.05%)	32 (0.08%)	33 (0.08%)	0	7 (0.29%)	4 (0.17%)

> 26 – 52 weeks	2,386	1,234	6 (0.25%)	4 (0.17%)	8 (0.34%)	3 (0.24%)	9 (0.73%)	5 (0.41%)
> 52 weeks	889	216	5 (0.56%)	13 (1.46%)	8 (0.90%)	1 (0.46%)	1 (0.46%)	3 (1.39%)
Totals	47,790	4,493	31 (0.06%)	52 (0.11%)	51 (0.11%)	4 (0.09%)	17 (0.38%)	13 (0.29%)

Among the 4493 subjects treated with a comparative agent (including placebo) in the 84 comparative studies, 4 (0.09%) subjects experienced CHF events, 17 (0.38%) subjects experienced MI events and 13 (0.29%) subjects experienced stroke events.

Table 2 (below) further summarizes the treatment emergent, all causality incidence of selected cardiovascular events by drug category for 84 completed comparative studies.

Table 2: Treatment Emergent, All Causality Incidence of Selected Cardiovascular Events by Drug Category for 84 Completed Comparative Studies. (A subject may be counted under multiple drugs).

Drug Category	Total # of Subjects			
		Number(%) of Subjects with CHF	Number(%) of Subjects with MI	Number(%) of Subjects with Stroke
Doxazosin	5,281	9 (0.17%)	17 (0.32%)	15 (0.28%)
placebo	1,601	0	7(0.44%)	5 (0.31%)
Diuretic	483	1 (0.21%)	2 (0.41%)	3 (0.62%)
ACE-I	736	0	1 (0.14%)	2 (0.27%)
Beta blocker	555	0	0	0
CCB	381	0	0	0
Other	813	3 (0.37%)	8 (0.98%)	3 (0.37%)

Table 3 (below) further summarizes the treatment emergent, all causality incidence of selected cardiovascular events by drug category for the 17 BPH/urologic comparative studies.

Table 3: Treatment Emergent, All Causality Incidence of Selected Cardiovascular Events by Drug Category for 17 BPH/Urologic Comparative Studies. (A subject may be counted under multiple drugs.)

Drug Treatment	Total # of Subjects	Number(%) of Subjects with CHF	Number(%) of Subjects with MI	Number(%) of Subjects with Stroke
Doxazosin	2,584	6 (0.23%)	10 (0.39%)	8 (0.31%)
placebo	1,246	0	6 (0.48%)	5 (0.40%)
Other alpha blocker	238	0	2 (0.84%)	1 (0.42%)
finasteride	555	3 (0.54%)	6 (1.08%)	2 (0.36%)

Table 4 (below) further summarizes the treatment emergent, all causality incidence of selected cardiovascular events by drug category for the 67 cardiovascular completed comparative studies.

Table 4: Treatment Emergent, All Causality Incidence of Selected Cardiovascular Events by Drug Category for 67 Cardiovascular Comparative Studies. (A subject may be counted under multiple drugs).

Drug Category	Total # of Subjects			
		Number(%) of Subjects with CHF	Number(%) of Subjects with MI	Number(%) of Subjects with Stroke
Doxazosin	2,697	3 (0.11%)	7 (0.26%)	7 (0.26%)
placebo	355	0	1 (0.28%)	0
Diuretic	483	1(0.21%)	2(0.41%)	3(0.62%)
ACE-I	736	0	1 (0.14%)	2 (0.27%)
Beta blocker	555	0	0	0
CCB	381	0	0	0
Other alpha blocker	20	0	0	0

Table 5 (below) further summarizes the treatment emergent, all causality incidence of selected cardiovascular events by drug category for the 15 placebo controlled BPH / Urologic completed comparative studies.

Table 5: Treatment Emergent, All Causality Incidence of Selected Cardiovascular Events by Drug Category for 15 Placebo Controlled BPH / Urologic Studies (A subject may be counted under multiple drugs.)

Drug Treatment	Total # of Subjects			
		Number(%) of Subjects with CHF	Number(%) of Subjects with MI	Number(%) of Subjects with Stroke
Doxazosin	2,474	5 (0.20%)	10 (0.40%)	8 (0.32%)
placebo	1,246	0	6 (0.48%)	5 (0.40%)
terazosin	131	0	1 (0.76%)	0
finasteride	555	3 (0.54%)	6 (1.08%)	2 (0.36%)

Table 6 (below) further summarizes the treatment emergent, all causality incidence of selected cardiovascular events by drug category for the 12 placebo controlled cardiovascular studies.

Table 6: Treatment Emergent, All Causality Incidence of Selected Cardiovascular Events by Drug Category for 12 Placebo Controlled Cardiovascular Studies. (A subject may be counted under multiple drugs.)

Drug Category	Total # of Subjects			
		Number(%) of Subjects with CHF	Number(%) of Subjects with MI	Number(%) of Subjects with Stroke
Doxazosin	549	0	1(0.18%)	3(0.55%)
placebo	343	0	1(0.29%)	0
Diuretic	63	0	1(1.59%)	0
ACE-I	80	0	0	0
Beta blocker	36	0	0	0
Other alpha blocker	20	0	0	0

2) Studies referenced in the NDA for hypertension (NDA #19,688) filed to the U.S. FDA

The clinical trial data for the doxazosin hypertension NDA come from 45 trials involving 2,808 hypertensive subjects (1548 receiving doxazosin, 699 receiving active comparative therapy, and 561 receiving placebo). These 45 clinical studies provided substantial evidence that doxazosin is safe and effective in the treatment of hypertension. The incidence of the selected cardiovascular events of CHF, MI and stroke reported in all 45 clinical studies in the submission is consistent with that observed in the large pool of studies discussed under category 1 (above).

One of the 45 studies included in the doxazosin hypertension NDA was a twelve-week, double-blind, placebo-controlled parallel study which evaluated the use of doxazosin when added to a stable regimen of digoxin and diuretic in patients with congestive heart failure (doxazosin n=32; placebo n=35). Analysis of the data from this rigorous trial in a high risk patient population revealed that the doxazosin treated group had significantly less morbidity than the placebo group. Patients in the doxazosin group were significantly less likely to experience cardiac events than patients in the placebo group (0 vs 8; p=0.004). No patients in the doxazosin group were hospitalized for heart failure while 3 patients in the placebo group were hospitalized for heart failure. No patients in the doxazosin group suffered myocardial infarction while 2 patients in the placebo group suffered a myocardial infarction. There were also no deaths in the doxazosin group, compared with three sudden deaths in the placebo group.

3) Other studies

Adverse event information for CHF, MI, and stroke from other studies (defined above) available as of 15 May 2000 was reviewed. This additional information, from studies involving more than 60,000 patients, was consistent with the results discussed under category 1 (above).

Conclusion

This integrated review identified a rigorous database of over 47,700 subjects who had received doxazosin in 271 completed clinical studies, including the doxazosin GITS MAA submission for hypertension and BPH, as well as the doxazosin NDA submission for BPH. Review of these clinical study data from these 271 studies combined indicated a very low incidence ($\leq 0.11\%$) of each of the selected cardiovascular events (CHF, MI and stroke) among subjects taking doxazosin. The incidence of CHF, MI, and stroke events in Pfizer sponsored clinical trials was similar for doxazosin versus pooled comparative agents. Although the maintenance period on therapy was short relative to ALLHAT, the majority of the ALLHAT CHF events occurred in the first year, with separation between treatment groups beginning in the first few months. In the Pfizer clinical database, approximately 40,000 patients had a maintenance period on therapy of between 8 and 26 weeks, and approximately a further 2,300 of between 26 and 52 weeks. This should have been sufficient to demonstrate any adverse effect on cardiac function to explain the difference in CHF event rates in ALLHAT. It should be noted that patients in

the Pfizer database were on average about 10 years younger than those in ALLHAT, and had fewer CHD risk factors. In addition, the Pfizer studies included an initial washout period, which ALLHAT did not.

Additionally, a review of the rigorous database from the original doxazosin NDA submission for hypertension, which clearly demonstrated efficacy and safety, provided information consistent with the very low incidence of the selected cardiovascular events. One of the studies from this submission, a double-blind, placebo-controlled trial in high risk patients with CHF, showed a significant advantage of doxazosin over placebo for cardiovascular morbidity and mortality.

Overall, the review of the clinical trial data, from more than 100,000 subjects who received doxazosin / doxazosin GITS, indicates that there is no signal of a causal relationship between doxazosin and the selected cardiovascular events of CHF, MI, or stroke in Pfizer's databases.

Section 3: Review of Pfizer Early Alert Safety Database

Section 3 Summary

The Pfizer-sponsored clinical trial database is a rigorous source of data to monitor occurrences of congestive heart failure (CHF), myocardial infarction, and stroke. Although the review of the clinical trial data did not show any signal with regard to these selected cardiovascular events, a comprehensive review of the early alert safety database was undertaken for CHF or heart failure-like events, myocardial infarction-like events and stroke-like events as supportive evidence. As it is difficult to draw conclusions from adverse event data, these events are reported here in summary only. Full details of these cases are provided in Appendix 3.

Description of Early Alert Safety Database

Pfizer's early alert safety database contains cases of adverse events reported spontaneously to Pfizer, cases reported from adverse event registries, cases of adverse events published in the medical literature, and cases of serious adverse events reported from clinical studies regardless of causality.

Spontaneous reports by their nature are of lesser scientific rigor than clinical trial data. Limitations of spontaneous reporting includes duplicate and second-hand reporting; variable expertise of reporters; incomplete information reported including uncertain drug ingestion; unsubstantiated reports/anecdotes; inability to use reports to determine incidence; and inability to use reports to assess causality. However, spontaneous reports draw from very large number of patients, reflect real-world usage situations, and provide a means for detecting rare events that are not captured in usual clinical trials.

Methodology

The early alert safety database was reviewed for cases that involved cardiovascular adverse events entered into the database through 28 February 2001. For the purposes of this review, cardiovascular adverse events were defined as any event that coded to WHO-ART preferred adverse event terms listed under the "cardiovascular, general", "heart rate/rhythm", "myo-, endo-, pericardial & valve" and "vascular (extracardiac)" body systems, as well as the preferred adverse event terms "sudden death" and "pulmonary edema." For the purpose of this review, heart failure-like events were defined as events that coded to the WHO-ART preferred adverse event terms "cardiac failure", "cardiac failure left", "cardiac failure right", "cardiomegaly", "cardiomyopathy", "circulatory failure", "hypertension pulmonary", "pulmonary edema", and "worsening heart failure". Myocardial infarction or related events were defined as events that coded to the WHO-ART preferred adverse event terms "myocardial infarction", "myocardial rupture (post infarct)", and "thrombosis coronary". Stroke-like events were defined as events that coded to the WHO-ART preferred adverse event terms "cerebral hemorrhage",

“cerebrovascular disorder”, “embolism cerebral”, “hemorrhage intracranial”, “subarachnoid hemorrhage”, “thrombophlebitis cerebral vein”, “thrombosis carotid”, “thrombosis cerebral”, and “thrombosis cerebral arterial”.

For clinical study cases, the database was reviewed for doxazosin, doxazosin GITS, comparison agents, or blinded therapy cases from Pfizer-sponsored doxazosin or doxazosin GITS clinical studies. These cases were further reviewed for cases in which either the investigator or Pfizer attributed causality or relatedness of the event to doxazosin or doxazosin GITS. The doxazosin/doxazosin GITS cases were also reviewed for all cases where the patient was reported to have died regardless of causality. For non-clinical-study cases, the database was reviewed for doxazosin and doxazosin GITS cases.

Results/Discussion

A search of the Pfizer early alert safety database identified 99 serious Pfizer-sponsored clinical study cases with cardiovascular events in which the investigator and/or Pfizer attributed causality or relatedness of the events to doxazosin or doxazosin GITS therapy. The most commonly reported events (in 10 or more cases) among these 99 serious doxazosin/doxazosin GITS Pfizer-sponsored clinical study cases reporting adverse cardiovascular events (86 doxazosin and 13 doxazosin GITS) were angina pectoris / angina pectoris aggravated, cerebrovascular disorder, syncope, hypotension / hypotension postural, myocardial infarction/ thrombosis coronary, chest pain, and atrial / ventricular fibrillation. These events have been reported to be associated with doxazosin therapy, and are listed in the current doxazosin and doxazosin GITS labeling.^{1,2}

Of the 99 serious Pfizer-sponsored clinical study cases, seven involved heart failure-like events, 13 involved myocardial infarction, and 18 involved stroke-like events or related events. Due to multiple events in three cases, there were 34 cases that reported these three types of events. In nearly all 34 cases, the patients had a concomitant medication(s) or medical history suggestive of pre-existing cardiovascular disorders or other risk factors associated with these events. The treatment indication in all but one of the 34 cases was hypertension. Therefore, these patients appeared to be at high risk of developing heart failure, myocardial infarction, stroke, or related events independent of doxazosin or doxazosin GITS therapy, and there is no signal of a causal relationship between these events and doxazosin or doxazosin GITS therapy. In addition, based on review of the cases in which the patient was reported to have died regardless of causality, there is no signal indicating that doxazosin or doxazosin GITS therapy places patients at increased risk of death.

A search of the Pfizer early alert safety database identified a total of 11,359 doxazosin and doxazosin GITS non-clinical-study cases (10,656 cases and 703 cases, respectively) entered into the database as of 28 February 2001. These cases were reported over the 13 years that doxazosin has been commercially available and following approximately 4.1 billion patient-days of doxazosin therapy. This gives an estimated reporting rate of 2,770 cases/billion patient-days of therapy. About 30% of these cases met the reporting criteria for a serious case. The treatment indication cited for the majority of doxazosin/doxazosin GITS cases, was BPH (50%, 5,633 cases), with 29% of cases reporting hypertension as

the indication (3,329 cases). The patient's ages were reported to be ≥ 55 years in 60% of the cases, and the distribution of all individual cardiovascular adverse events in these cases was similar to that of all cases. Concomitant use of a diuretic and/or at least one other antihypertensive agent was reported in 29% of all cases, 26% of serious cases, 53% of cases where hypertension was reported as an indication, and in 20% of cases where BPH was the indication.

A total of 148 cases of heart failure-like events were reported, representing 1.3% of all doxazosin/doxazosin non-clinical study cases, with a reporting rate of about 36 cases/billion patient-days of therapy. Of the 58 relevant non-clinical-study cases reporting heart failure-like events, the majority was male and elderly. This is not entirely unexpected, since heart failure is more common in men and in the elderly.^{3,4} Most of these cases, as with the Pfizer-sponsored clinical study cases, were treated with fairly low daily doses of doxazosin or doxazosin GITS suggesting that due to possible suboptimal dosing, hypertensive patients and BPH patients with a history of hypertension could have had their blood pressure inadequately controlled at the time of the events. Most of the cases had medical histories that appear to have placed the patients at high risk for heart failure-like events. The number of cases where the indication for use of doxazosin/doxazosin GITS was BPH was slightly higher than the number of cases where the indication was hypertension. Separate review of the cases of heart failure-like events where the indication was BPH found that these cases were mostly elderly and also had medical histories suggestive of high risk for these events. It is not entirely unexpected that at least some BPH patients treated with doxazosin/doxazosin GITS would be at high risk for heart failure-like events. Since the prevalence of BPH increases with age,⁵ it is not unexpected that at least some BPH patients would have concurrent cardiovascular disease that would be associated with an increased risk of heart failure, as well as for myocardial infarction and stroke. Also, for the 11 cases where the patients died as a result of the heart failure-like events, the patients were mostly males and elderly, and many were reported to have medical histories that would place them at high risk of heart failure-like events.

Acute myocardial infarction is one of the most common diagnoses in hospitalized patients in industrial nations.⁶ Of the non-clinical study cases reported to Pfizer, there were 154 non-clinical study cases reporting myocardial infarction-like events which were reviewed. These 154 cases represent 1.3% of all doxazosin/doxazosin non-clinical study cases, with a reporting rate of about 38 cases/billion patient-days of therapy. Of these 154 cases, 112 (88%) were indicated for BPH. This dataset was notable for the nearly 75% of cases originating from marketing-based patient compliance programs. These were reported by consumers and most lacked information regarding concomitant medication and medical history. Most of these patients were male, age ≥ 51 years, and had risk factors for developing myocardial infarction-like events independent of doxazosin or doxazosin GITS therapy, based on significant medical histories and relevant concomitant therapies. This dataset was notable for the nearly 75% of cases originating from market-based patient compliance programs. These were reported by consumers and most lacked information regarding concomitant medications and medical history. There were 54 patients who were reported to have died, and this outcome did not appear to be associated

with doxazosin therapy in these cases. The mortality rate of acute myocardial infarction is approximately 30% with more than half of these deaths occurring before the patient even reaches the hospital.⁶ Given that most patients were at risk for myocardial infarction-like events, and the majority of these cases originated from marketing-based patient compliance programs and were lacking key information regarding concomitant medication and/or medical history, there was no signal of a causal relationship with doxazosin or doxazosin GITS.

Stroke events occur predominately in the middle to later years of life with the incidence of stroke increasing with age. Hypertension is also a risk factor of great importance.⁷ There was a total of 170 non-clinical study cases reporting stroke-like events, representing 1.7% of all doxazosin/doxazosin non-clinical study cases, with a reporting rate of about 46 cases/billion patient-days of therapy. Not surprisingly, most of these patients were male and age ≥ 51 years. Also, the majority of patients had a medical history or were taking medication(s) suggestive of concurrent illness that could have predisposed them to the reported events independent of doxazosin and doxazosin GITS therapy. In most cases, the daily dose was low, suggesting that due to possible suboptimal dosing, some of the patients could have had inadequately controlled blood pressure at the time of the events. This dataset was notable in that over half of the cases (89/170) originated from market-based patient compliance programs. For the 37 cases in which the patient was reported to have died, this outcome did not appear to be associated with doxazosin/doxazosin GITS therapy. These were reported by consumers and most lacked information regarding comedication and medical history. Overall, there was no signal of a causal relationship between stroke-like events and doxazosin/doxazosin GITS therapy.

Conclusion

The number of cases reported to Pfizer that involved heart failure-like events, myocardial infarction-like events, and stroke-like events was small compared to all reported cases of adverse events, and the characteristics of the patients suggest that they were at high risk of experiencing these selected cardiovascular events independent of doxazosin/doxazosin GITS therapy. The number of these cases is very small considering the more than 4.1 billion patient-days of doxazosin therapy over 13 years of worldwide commercial use. Review of the cases of heart failure-like events, myocardial infarction-like events, and stroke-like events supports the conclusion of the review of Pfizer's clinical trial databases that there is no signal of a causal relationship between these select cardiovascular events and doxazosin or doxazosin GITS therapy. In addition, based on review of all cases in which the patient was reported to have died, there is no signal indicating that doxazosin or doxazosin GITS therapy places patients at increased risk of death.

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Section 4: Prescription Event Monitoring for Doxazosin

Section 4 Summary

A Prescription-Event Monitoring (PEM) study of 8,482 patients in the United Kingdom who had been treated with doxazosin between March 1989 (when doxazosin was first marketed in the United Kingdom) and January 1991 was finalized in January 1995. The rates of events occurring during the first month of treatment were compared with the mean rates recorded during the second to sixth month of treatment. These data were compared with those obtained during PEM studies of seven other drugs also used in the treatment of hypertension and with 'pooled' data. Among the 8,482 patients, the mean age was recorded as 59.3 and the male to female ratio was noted to be 0.8 and where indication was stated, 99% of the patients had received doxazosin for hypertension. The event rates (per 1000 patients) during the first month of therapy with doxazosin were cardiac failure, 0.5; cerebrovascular accident, 0.2; and ischaemic heart disease, 1.5. The general pattern of these events was consistent with those observed in other PEM studies of antihypertensive agents. The PEM report concluded that "no serious non-fatal events and no deaths were attributed to doxazosin" and they concluded that doxazosin was a safe drug for use in the treatment of hypertension.

A Prescription-Event Monitoring (PEM) study of 8,482 patients who had been treated with doxazosin between March 1989 (when doxazosin was first marketed in the United Kingdom) and January 1991 was finalized in January 1995. PEM is the principal activity of the Drug Safety Research Unit (DSRU), operating as a charitable trust in association with University of Southampton, Southampton, England. In PEM, general practitioners in the U.K. are requested to report all significant events that are recorded in the patient's notes after treatment with a new drug. PEM facilitates the collection of information about groups of patients using drugs prescribed in 'real life' conditions, providing valuable data for the assessment of the safety of new drugs and information about the pattern of morbidity and mortality in the general population.

The rates of events occurring during the first month of treatment were compared with the mean rates recorded during the second to sixth month of treatment. The calculation of rates was restricted to those events which had been experienced by nine or more patients during the first month of treatment (rates in excess of one per thousand). A 'signal' was noted when this rate exceeded the second to sixth month rate by a factor of three or more or when the first month rate exceeded a pooled base-rate for other drugs by a similar amount. These data were compared with those obtained during PEM studies of seven other drugs also used in the treatment of hypertension (specifically, nicardipine, amlodipine, isradipine, betaxolol, enalapril, lisinopril and ramipril) and with 'pooled' data derived from these eight studies and 31 other PEM studies. The 'pooled' data from

all 39 studies provide background or 'base-line' information of the frequency of adverse events in various populations.

PEM defines an event as any new diagnosis, any reason for consultant referral, hospital admission, any unexpected deterioration (or improvement) in a concurrent illness, any suspected drug reaction or any other complaint considered to be of sufficient importance to note in a patient's record. An indication which is mentioned in the events section of the PEM form is not coded as an 'event'. The events are recorded irrespective of whether or not a patient was still taking the drug.

Among the 8,482 patients summarized in the PEM study, the mean age was recorded as 59.3 and the male to female ratio was noted to be 0.8. The age and gender distribution reported for doxazosin was consistent with that reported for four other antihypertensive agents in other PEM studies. Where indication was stated, 99% of the patients had received doxazosin for hypertension while the remaining 1% included small numbers of patients with other conditions such as angina or cardiac failure. The majority (90%) were treated with ≤ 4 mg/d.

The relevant event rates (per 1000 patients) during the first month of therapy with doxazosin were noted as follows:

Cardiac failure	0.5
Cerebrovascular accident	0.2
Ischaemic heart disease	1.5

The general pattern of these events was consistent with those from that observed in other PEM studies of other antihypertensive agents. The reporting rate of these events during the first month compared to the rate for the second to sixth month did not provide a signal of a causal relationship with doxazosin therapy. This is also consistent with the results of PEM studies of other antihypertensive agents.

The causes of death were established for 150 (88%) of 170 cases; 65 occurred during the first six months of starting treatment with doxazosin. Ischaemic heart disease, cerebrovascular accidents and cancer accounted for the majority and no deaths appeared to have been related to treatment.

The PEM report concluded that "no serious non-fatal events and no deaths were attributed to doxazosin" and they concluded that doxazosin was a safe drug for use in the treatment of hypertension. The approximate 10,000 patients included in most PEM studies is sufficient to detect events with a true frequency in excess of about one in three thousand with reasonable certainty, provided the background rate for the same event is low.

The final PEM study report dated January 1995 is attached in Appendix 4.

Section 5: Review of Medical Literature

Section 5 Summary

As most Pfizer sponsored clinical trials involving doxazosin / doxazosin GITS were less than 1 year in duration, the literature was reviewed with particular focus on long term data involving the use of doxazosin for one year or greater.

Publications of long term clinical trials (at least one year in duration) involving treatment with doxazosin and publications (clinical trials or review articles) that included mention of both doxazosin and heart failure in humans were identified. A review of the 22 clinically relevant publications revealed that among 5,919 clinical trial subjects, 23 (0.38%) subjects had an adverse event of CHF, 42 (0.71%) had an adverse event of myocardial infarction, and 26 (0.44%) had an adverse event of stroke. Review of the medical literature supports the conclusion that there is no safety signal regarding CHF, MI, or stroke in subjects treated with doxazosin for either hypertension or benign prostatic hyperplasia (BPH) in Pfizer's clinical databases.

Methodology

A search of Medline (1966 to 13 March 2001) and Embase (1974 to 13 March 2001) was conducted for published clinical studies in which doxazosin was administered for periods of 52 weeks or longer. Eighteen studies (22 publications) were identified for review, including one study in which the active treatment period was 46 weeks rather than 52. The publications were reviewed for any mention of patients who experienced congestive heart failure (CHF), myocardial infarction, or stroke. Copies of the publications are included in Appendix 5A.

A search of Medline (1966 to 13 March 2001) and Embase (1974 to 13 March 2001) was also conducted for publications that included doxazosin and heart failure in humans. This search was not limited by duration of therapy. Seven publications were identified for review and are included in appendix 5B. Two of the 7 publications (Martinez-Castelao *et al* and Stokke *et al*) were also identified in the search described in the paragraph above. The additional 5 publications included two review articles on alpha-blockers, and one article and two abstracts on clinical trials using doxazosin in subjects with CHF.

Results

A total of 5919 subjects received treatment with doxazosin in the pooled published studies, although not all subjects received doxazosin for at least one year. Of these 5919 subjects, 23 (0.38%) subjects had an adverse event of CHF, 42 (0.71%) subjects had an

adverse event of myocardial infarction, and 26 (0.44%) subjects had an adverse event of stroke.

The majority of the 5919 subjects were enrolled in a one-year surveillance study conducted in Norway (Stokke *et al*). Of the 4,260 hypertensive subjects treated with doxazosin in this Norwegian study, 23 (0.54%) experienced cardiac insufficiency (1 fatal), 35 (0.82%) had myocardial infarction (7 fatal), and 26 (0.61%) experienced stroke (5 fatal). There was also one death due to pulmonary edema and three sudden deaths.

In the publication by Andersson *et al*, one subject withdrew from the trial due to recurrent transient ischemic attacks, however, the treatment group (doxazosin or atenolol) was not specified in the publication. In the TOHMS study (Grimm *et al*) which measured the incidence of cardiovascular events over an average of 4.4 years of follow-up, three subjects died due to coronary heart disease, 16 had nonfatal myocardial infarction, two experienced congestive heart failure, and five experienced stroke. All of these cardiovascular events occurred in subjects receiving an active drug treatment (doxazosin, amlodipine, acebutolol, chlorthalidone, or enalapril). However, the specific drug treatment was not provided in the publication.

DiBianco *et al* reported on the use of 12 weeks of treatment with doxazosin (n=32) versus placebo (n=35) added to a stable regimen of digoxin and diuretic in patients with CHF. This study is also included as part of the review of the Pfizer sponsored clinical trial data. Patients in the doxazosin group were significantly less likely to experience cardiac events than patients in the placebo group (0 vs 8; p=0.004). No patients in the doxazosin group were hospitalized for heart failure while 3 patients in the placebo group were hospitalized for heart failure. No patients in the doxazosin group suffered myocardial infarction while 2 patients in the placebo group suffered a myocardial infarction. There were no deaths in the doxazosin group, compared with three sudden deaths in the placebo group.

Kalman *et al* and Kukin *et al* reported on the use of doxazosin as an adjunct to beta blocker therapy in patients with CHF. These publications address the issue of hemodynamic tolerance to chronic alpha blockade. The review article by Frishman *et al* discusses the use of alpha blockers in patients with CHF and refers to the study by Kukin *et al*. However, there is no mention of adverse events of CHF in hypertensive or BPH patients. The review article by Carruthers *et al* discusses adverse effects of alpha1-adrenergic blocking drugs but there is no mention of CHF in hypertensive or BPH patients.

Conclusion

A review of the published medical literature supports the conclusion that there is no safety signal regarding the occurrence of CHF, MI, or stroke in patients treated with doxazosin for either hypertension or BPH in Pfizer's clinical databases.

Section 6: Other Relevant Information

Doxazosin is also indicated for the treatment of Benign Prostatic Hyperplasia (BPH). The Medical Therapy of Prostate Symptoms (MTOPS) trial is an ongoing multicenter, double-blind NIH-sponsored trial involving about 2,800 patients with BPH treated with either doxazosin, finasteride, the combination of doxazosin and finasteride or placebo. The planned duration of follow-up is 4-6 years. To date, the minimum follow-up period is 2 years. The study is anticipated to be completed by the year 2002.

In light of the preliminary ALLHAT findings, an independent committee reviewed data from the MTOPS trial for cardiovascular disease endpoints. The Committee found that:

- There is a low absolute risk of congestive heart failure across the trial.
- There is no significant difference in the incidence rates of congestive heart failure among the various treatment arms. It was recognized, however, that because of the small number of events the confidence intervals around these rates were quite large.
- Based on their review of the data, the Committee did not recommend changes to the trial protocol.

Documentation of the independent committee's findings is provided in Appendix 6.

Section 7: Conclusion

After review of the preliminary ALLHAT data available and based upon Pfizer's reviews of its clinical trial data, early alert safety database, and the medical literature, Pfizer believes that doxazosin remains a safe and effective therapeutic option for hypertension and/or benign prostatic hyperplasia as currently labeled. This position is further supported by Pfizer's extensive experience with doxazosin for more than 13 years, both in marketing the product (>4.1 billion patient-days of doxazosin therapy worldwide) and in our clinical trial program, the majority of which was performed with doxazosin monotherapy.

Pfizer concurs with current hypertension treatment guidelines (including JNC VI, WHO-ISH and other country-specific guidelines) that stress the importance of achieving goal blood pressure. In certain patient populations, such as diabetic patients, more stringent blood pressure goals are recommended. The treatment guidelines include doxazosin as one of the recommended therapeutic options.

Pfizer continues to support ALLHAT as an important study of the effects of blood pressure and lipid lowering on morbidity and mortality in cardiovascular disease.

Pfizer will continue to monitor doxazosin clinical trials and post-marketing surveillance in keeping with good pharmacovigilance practice and regulatory requirements.