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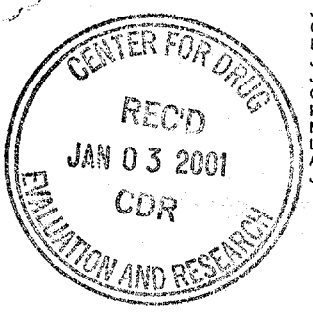
DIRECT LINE:

01 JAN -4 A11

January 2, 2001



BY HAND

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1-23
12420 Parklawn Drive
Rockville, MD 20857

Re: Citizen Petition

Dear Sir or Madame:

Enclosed for filing please find an original and four copies of the Citizen Petition and Compendium of Sources of Lawrence D. Bernhardt and Arnold Liebman. In addition, please file stamp the office copy.

Sincerely,

Susan M. Greenwood

Susan M. Greenwood

01P-0010

CP 1

January 3, 2001

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1-23
12420 Parklawn Drive
Rockville, MD 20857

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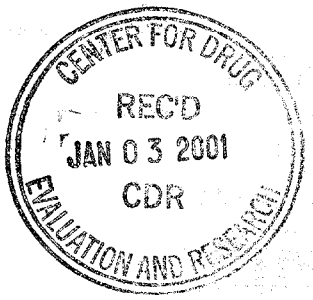

On May 30, 2000 and June 13, 2000, Lawrence D. Bernhardt and Arnold Liebman ("Petitioners") filed a civil class action lawsuit in the United States District Court for the Southern District of New York seeking, *inter alia*, injunctive relief in the form of emergency notice, described in more detail below, to be sent to patients in the United States who have ingested or are ingesting Cardura brand doxazosin mesylate tablets ("Cardura") manufactured and marketed by Pfizer, Inc. ("Pfizer"). Petitioners represent all persons who have used Cardura in the United States for the treatment of hypertension.

In a Memorandum and Order dated November 16, 2000, United States District Court Judge Lawrence M. McKenna has instructed Petitioners to first seek relief from the United States Food and Drug Administration ("FDA"). Petitioners therefore submit this Citizen Petition to the FDA pursuant to 21 C.F.R. § 10.30.

Because this petition constitutes a referral from the court under 21 C.F.R. § 10.60, Petitioners, FIRST, request that the FDA promptly notify them whether the agency will agree or decline to accept the referral from the court. See 21 C.F.R. § 10.60(b). More particularly, because the action requested herein constitutes an emergency safety notification to persons who are at immediate risk of death or grave personal injury, Petitioners request prompt notification of whether the FDA can and will answer this petition within the 180 days provided for under FDA

01P-0010

CP 1

regulations. 21 C.F.R. § 10.30(e). If the Commissioner of Food and Drugs determines that the FDA cannot or will not answer this petition within the time frame required by FDA regulations, Petitioners request that, pursuant to 21 C.F.R. § 10.60(b), the FDA promptly decline the referral of this matter from the court and permit the issue of emergency notification to be tried before the court.

CITIZEN PETITION

Petitioners submit this petition to request the FDA to require notice to the medical community and users of Cardura for the treatment of hypertension of the findings of the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial ("ALLHAT") conducted by the National Heart Lung and Blood Institute ("NHLBI") which demonstrates that users of Cardura are twice as likely to be hospitalized for congestive heart failure and have a higher chance of suffering from certain serious cardiac events, including strokes, as compared with patients taking the more traditional and less costly diuretic drug, chlorthalidone, to treat hypertension.

Specifically, Petitioners request that the FDA require Pfizer to issue a mailing under 21 C.F.R. § 200.5 and that the FDA similarly notify all patients in the United States who have ingested or are ingesting Cardura for hypertension by press release or "Talk Papers." The FDA should also require the insertion of a boxed warning on the labeling of Cardura (and of generic doxazosin mesylate tablets), and require such additional labeling changes (including changes in the approved indication, warnings, precautions, and contraindications) as the agency may deem appropriate.

In connection with the agency's review of this petition, Petitioners further request that the FDA bring the issues raised by the ALLHAT study and the relief requested in this petition before the agency's Cardio-Renal Advisory Committee for their review and input, pursuant to 21 C.F.R. §§ 10.60(c)(2) and 10.65. Petitioners, by their representatives, specifically request the opportunity to address that committee. Petitioners ask to be notified promptly whether the agency will schedule such a meeting.

STATEMENT OF GROUNDS

A. Cardura Is A Leading Drug For Pfizer

Pfizer is a Delaware Corporation with its principle place of business in New York, New York. Pfizer produces, distributes, and markets the anithypertensive drug doxazosin mesylate under the brand name Cardura. Cardura received FDA approval in 1990 and since then has been consistently marketed as a highly effective, "first-line" drug to treat hypertension. Ex. 1 and Ex. 2 (Feczko Tr. at 116 -117). Cardura's current label states that Cardura may be used alone or in combination with other drugs to treat hypertension. Cardura's annual sales approach $800,000,000 worldwide, at least half of which is for the treatment of hypertension alone. Ex. 4.

B. The ALLHAT Study

In 1994, the NHLBI began ALLHAT, an eight-year high blood pressure study. ALLHAT compared Cardura with the more traditional and less costly diuretic drug, chlorthalidone, used to treat hypertension. ALLHAT represented the single largest clinical trial to compare antihypertensive drugs over a long-term period and was specifically designed to address whether the benefit of the drugs were the same. See Ex. 26 (Furberg Affidavit); Ex. 25 (Krakoff

Affidavit.) "Whilst the alpha blockers have been available to a great many years they have never been subjected to a long-term outcome trial in hypertension." Ex. 5. Dr. Claude Lenfant, NHLBI Director stated: "No large-scale blood pressure treatment study had ever compared these 2 classes of drugs. Earlier studies were small and could not, for example, detect an increase in patients' risks of congestive heart failure." Ex. 6. Pfizer contributed $30 million to the ALLHAT study. Ex. 2 (Feczko Tr. at 134). Pfizer also assisted the NHLBI in its enrollment effort. Id. at 132. Pfizer played an integral role in ensuring that ALLHAT met its full enrollment, thus ensuring that the ALLHAT study would proceed. Id.

C. The ALLHAT Adverse Findings

On February 2, 2000, Dr. Joseph Feczko, the senior vice president for medical and regulatory operations of Pfizer, attended a meeting at the NHLBI. During that meeting, Dr. Feczko learned that the Cardura arm of ALLHAT was being stopped early due to adverse findings. Ex. 2 (Feczko Tr. at 16). On March 8, 2000, the NHLBI publicly announced that it had stopped the part of the ALLHAT trial concerning Cardura early because it had found that users of Cardura were twice as likely to be hospitalized for congestive heart failure and had a higher chance of suffering from certain other serious cardiac events, including strokes, than users of the diuretic drug chlorthalidone.[1] Due to these finding, the NHLBI immediately offered patients on Cardura alternative medication. Ex. 7. At the American College of Cardiology ("ACC") meeting in March 2000, ALLHAT's Study Chairman, Dr. Curt Furberg, made a presentation in which he stated that: "Doxazosin (Cardura) is not recommended as first-line

[1] The ALLHAT findings were published in the April edition of the Journal of American Medical Association ("JAMA"). See Ex. 26 (Exhibit B).

therapy" for the treatment of hypertension. Ex. 8. On March 15, 2000 in response to the NHLBI findings, ACC issued a rare clinical alert recommending that "physicians discontinue use of a widely prescribed drug [Cardura] for the treatment of hypertension." Ex. 19. The ACC's alert further stated: "The ACC encourages physicians who treat hypertensive patients to review the new data with their colleagues to ensure the rapid dissemination of this important information." Id. The ACC issued a second clinical alert on March 23, 2000, warning physicians to reassess carefully the use of Cardura in treating patients for hypertension due to the findings of the NHLBI-sponsored study. Ex. 9.

D. The Results Of The ALLHAT Study Are Not Well Known And Pfizer Has Taken Steps To Minimize This Important Information

While Pfizer publicly stated that it supported the NHLBI's decision to discontinue the Cardura part of the ALLHAT study (Ex. 10), Pfizer has taken no affirmative steps to communicate this critical information to medical practitioners or Cardura users or to revise its Cardura drug labeling in that regard or to issue any warning. Neither the prescribing information for Cardura nor Pfizer's website make any reference to the NHLBI findings or the ACC clinical alert or the critical implications thereof. For example, Pfizer's Internet website continues to state as follows: "Cardura may be used alone or in combination with diuretics . . ." (Emphasis added.) Cardura's U.S. Product Prescribing Information, which appears in the Physicians' Desk Reference, contains the same language found on Pfizer's Internet website, again without any reference to the NHLBI findings or the ACC clinical alert.

Pfizer, in fact, has taken very aggressive steps to minimize any decline in Cardura sales following the release of the adverse ALLHAT findings and to protect its annual $800 million of

Cardura sales. Among other things, even though Pfizer still does not know the answer to whether or not ALLHAT's adverse results demonstrate that "Cardura is doing something negative" to cause a doubled risk of congestive heart failure (Ex. 11[2] and Ex. 2 (Feczko Tr. at 82),[3] it continues to aggressively assure all "high-prescribers of Cardura" that Cardura is an "exceptionally safe drug" (id., Ex. 12 and Ex. 2 (Feczko Tr. at 92-93)).

Moreover, following the release of the adverse ALLHAT findings, Pfizer made a conscious decision "not to issue a [public] statement" on the ALLHAT results, because doing so "would likely draw more media attention to the situation." Id., Ex. 13. Nor did Pfizer issue any information to physicians prescribing Cardura, unless the physicians first contacted Pfizer. Id., Ex. 14 and Ex. 2 (Feczko Tr. at 46). See also id., Ex. 2 (Feczko Tr. at 86) ("there's no warning letter"). Dr. Feczko testified that "[t]he [sales] representatives to the best of my knowledge are not proactively discussing ALLHAT." Ex. 2 (Feczko Tr. at 46). The adverse ALLHAT results were considered by Pfizer to be a "potential threat" to its business, whether they be in the hands of its "competitors," "governments . . . requesting labeling or price changes" or the "press." Ex. 3.

---

[2] This same internal Pfizer document acknowledges that the patients in ALLHAT are representative of the Cardura patient population. See id. ("ALLHAT, however, randomized elderly hypertensive patients without overt or apparent heart failure. (A patient population where Cardura is frequently used.")).

[3] See also id., Ex. 17 (Krakoff Tr. at 66-68). A article appearing in the Cleveland Clinic Journal Of Medicine, also notes that it was not possible to determine whether Cardura "cause[s] heart failure or just prevent[s] it less" and recommends that Cardura "not be used as monotheraphy in managing stage 1 or 2 hypertension." Ex. 18.

The results of all this lack of information were also carefully studied by an outside research agency retained by Pfizer. Id., Ex. 15 and Ex. 16. The research into ALLHAT "awareness" among Cardura prescribing physicians revealed that:

- "[Primary Care Physicians'] awareness and knowledge of ALLHAT is very low." Out of the Primary Care Physicians interviewed, none were aware of ALLHAT on an "unaided basis" and even those whose knowledge of ALLHAT could be "aided" by the researchers, had "very little knowledge about the trial."
- "The great majority of the Cardiologists . . . know next to nothing about the trial."
- "[Urologists'] knowledge of ALLHAT's preliminary results among those aware of the trial is minimal."

Id., Ex. 15 (emphasis added). In conclusion, the research reported that "knowledge of the trial's preliminary results is minimal for all specialties." Id. (emphasis added). Similar results were seen in "Wave 2" of the research conducted one full week later, or two weeks after the NHLBI announcement of the adverse ALLHAT findings. Id. Ex. 16. International awareness of ALLHAT was even worse. Id., Ex. 15 and Ex. 16 (showing 0% awareness levels for nearly all medical specialties).

Despite these results, Pfizer continued its practice of only providing information about ALLHAT "when asked" which was not that often. See, e.g., id., Ex. 2 (Feczko Tr. at 46) ("The [sales] representatives to the best of my knowledge are not proactively discussing ALLHAT"). Of course, Pfizer continues to assure all "high-prescribers of Cardura" that Cardura is an

"exceptionally safe drug" (id., Ex. 12), notwithstanding the heightened risk of congestive heart failure evidenced by the ALLHAT study.[4]

E. Pfizer's Lack Of Warnings Conflicts With The NHLBI And ACC

Pfizer's lack of informative notification is in contradiction with the unbiased and more responsible position taken by the NHLBI which stated that all high blood pressure patients taking Cardura (beyond those enrolled in ALLHAT) should be advised to "consult with their doctors about a possible alternative." Id., Ex. 6.[5] Before issuing that statement, the NHLBI notified each and every ALLHAT participant taking Cardura of the study's findings and immediately discontinued their use of the drug. Id.[6]

Similarly, Pfizer has taken no steps to advance the "clinical alert" issued by the American College of Cardiology (the "ACC"), advising physicians to "carefully reassess" Cardura use (id., Ex. 9).[7]

Petitioner's requested notice is fully consistent with the communique sent by the NHLBI to all Cardura users in the ALLHAT study and with the ACC's clinical alert. Each of these authoritative bodies have been flatly ignored by Pfizer in an effort to protect sales of Cardura,

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[4] A chart summarizing ALLHAT's adverse findings, appearing in the Cleveland Clinic Journal Of Medicine article submitted by Pfizer is attached hereto as Exhibit 18.

[5] Pfizer's own expert, Dr. Pool, agrees at least with regard to hypertensive patients he categorizes in the highest risk group, "Group C," that notice to patients "actually could be very valuable because it could -- the ALLHAT trial -- and even the questions about [Cardura] in the ALLHAT trial can be -- could be very valuable for the Cs to refocus physicians and their patients on what we really know." Id., Ex. 20 (Pool Tr. at 119-20).

[6] The ALLHAT study included 42,448 patients with hypertension, nearly 10,000 of which were treated with Cardura. Ex. 26 (Furberg Affidavit, Exhibit B).

[7] This refers to the second clinical alert issued by the ACC, on March 23, 2000, which was even less demonstrative than the first release issued by the ACC, on March 15, 2000, recommending that doctors "discontinue" their use of Cardura. See Exs. 9 and 19.

one of its "Magnificent 7" products (id., Ex. 3 and Ex. 2 (Feczko Tr. at 28, 122-23)). After all, the adverse ALLHAT results were considered by Pfizer to be a "potential threat" to its business, whether they be in the hands of its "competitors," "governments . . . requesting labeling or price changes" or the "press." Id., Ex. 3.[8]

F. The Implications Of ALLHAT Are Very Serious And Concern All Cardura Users Afflicted By Hypertension

Pfizer's conduct is particularly troubling given the serious implications of the ALLHAT findings, for all Cardura users afflicted by hypertension. See Ex. 25 (Krakoff Affidavit); Ex. 26 (Furberg Affidavit). Both of these experts, Dr. Krakoff, Petitioners' expert, and Dr. Furberg, the Chairman of the ALLHAT Steering Committee, have opined that as a result of ALLHAT's findings, Pfizer should be required to notify physicians and Cardura users that Cardura should no longer be prescribed as a "first line" drug to treat hypertension in any patient population.[9] Dr. Furberg has further opined that: "Pfizer's delay in providing such notification may every year cause thousands of unnecessary cases of heart failure among the large number of hypertensive patients who currently use Cardura." Ex. 26 (Furberg Affidavit).

Similarly, in the editorial published along with the adverse ALLHAT findings in the Journal of American Medical Association ("JAMA"), Dr. Louis Lasagna reported that the ALLHAT results "have major implications for the recommendations for treatment of

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[8] Pfizer has been in contact with the FDA concerning the ALLHAT findings. As the FDA informed Pfizer that it need not take any immediate action, Pfizer has been free to minimize the ALLHAT findings and concentrate on sales figures.

[9] Since submitting his affidavit, Dr. Krakoff has testified that all of his patients taking Cardura as a monotherapy to treat hypertension before the adverse ALLHAT results were released have been provided with alternative medications (id., Ex. 17 (Krakoff Tr. at 45-46) and he has removed Cardura as an "add-on" drug therapy wherever possible (id., Ex. 17 (Krakoff Tr. at 48-49). See also id., Ex. 17 (Krakoff Tr. at 76-77).

hypertension, which currently include [Cardura] as a first-line agent." Ex. 21. Dr. Franz Messerli of the Oschler Institute similarly reported in The Lancet that the guidelines for treating hypertension "have to be amended to the effect that [Cardura], or the whole class of peripheral [alpha]-blockers, should no longer be considered as first-line antihypertensive therapy" and "[w]hether [Cardura] should continue to be used as add-on antihypertensive therapy remains to be determined . . . although it probably should be avoided . . . ." Ex. 22. Pfizer, nonetheless, continues to advertise Cardura as a first-line drug for treating hypertension "either alone or in combination." Ex. 1 and Ex. 2 (Feczko Tr. at 116-17).

In an article entitled "What You Don't Know" (Ex. 24) an investigative reporter summarized this situation as follows:

> In the case of Cardura, the alpha-blocker removed from the NIH blood-pressure trial on March 8, the system still failed even when individual parts of it performed well. When the Cardura patients had to be taken off the drug, the National Heart, Lung, and Blood Institute issued a press release that included the most newsworthy particulars. One week later, Curt Furberg, the chair of the study, made a detailed presentation at the annual meeting of the American College of Cardiology in California. . . . The American College of Cardiology took the finding a step further, issuing a press statement urging doctors "to discontinue use" of Cardura and other alpha blockers for treating blood pressure. This seemed to be one of the clearest drug warnings ever issued by an expert medical group. But only hours later, the American College of Cardiology was saying that it had made a mistake and was not in fact urging doctors to discontinue the drug.
>
> * * *
>
> Pfizer asked the college to issue a new release, making it clear that it was not urging doctors to discontinue use of the drug. The cardiology group agreed, according to both Pfizer and Caudron.[10]

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[10] The author of this article further noted that Pfizer contributes over $500,000 to the ACC per annum. See also Ex. 23 ("We have been successful in getting the ACC to agree to a clarification . . .").

> Pfizer then made the new press release available to its sales force to use when talking to doctors who might now express concern about Cardura, says Michael Widlitz, medical group director for Pfizer.
>
> Widlitz says Pfizer agreed with and supported the findings of the NIH study. Cardura should not be a first-choice or principal blood-pressure drug, he says. . . . But Widlitz concedes that the company had issued no warning letter to doctors about the findings, had prepared no brochure, and had not put anything in the product's package labeling.

In summary, the author concluded that there has been no change in medical practice or decrease in Cardura sales following ALLHAT:

> More than two months after the warning about Cardura, there is no evidence that the new findings had any measurable effect on medical practice. Cardura's sales were unchanged throughout the period, according to data from IMS Health. News coverage was minimal. And the one clear warning from the American College of Cardiology had become garbled.

Id., Ex. 24.[11]

* * *

The above-quoted report is consistent with this statement of grounds and demonstrates that material information regarding a very serious public health risk has not been provided to Cardura users or practitioners and that the perceptions of that group continued to be directed by Pfizer toward "business as usual."

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[11] The author of this article points out that: "US law does not provide for the long-term testing of drugs, before or after approval for marketing. Even when occasional long-term tests reveal unexpected problems, no reliable way exists to ensure that patients are promptly taken off drugs that are shown to be dangerous, weak, or ineffective. Even when lives are at stake, drug companies and other health authorities repeatedly have failed to warn doctors and patients about newly discovered problems or ensure they halt treatment or switch to a better drug." Id.

G. The FDA Has The Authority To Issue Notice To The Medical Community And To Cardura Users

The Food and Drug Administration (the "FDA") has a Congressionally mandated mission to "protect the public health by ensuring" that "human drugs . . . are safe and effective." 21 U.S.C. § 393. To this end, the FDA has authority to regulate the labeling of human drugs. Id. Labeling is defined as "all labels and other written, printed, or graphic matters (1) upon any article or any of its containers or wrappers, or (2) accompanying such article." 21 U.S.C. § 321(m). Labeling "includes not only package inserts, but also separate communications concerning the drug, such as "Dear Doctor" letters sent by the drug manufacturers to physicians to provide information about a drug." Walls v. Armour Pharm. Co., 832 F. Supp. 1467, 1482-83 (M.D. Fla. 1993). The FDA's control over drug labeling allows for the dissemination of notice of the ALLHAT findings to the medical community in the form of a "Dear Health Care Professional" letter. 21 C.F.R. § 200.5.

ALLHAT has disproved the popular notion that alpha-blockers were a superior treatment for hypertension. Ex. 20 (Pool Tr. at 60:23-25; 61:2-5 ("I have to face the harsh reality that - of what ALLHAT says, that is that all of the clinical hypotheses that we put forth, we could not prove in ALLHAT that Doxazosin was superior to Chlortalidone as an antihypertensive monotherapy for treatment of hypertension in high risk patients.")). ALLHAT has showed that Cardura is no more effective that a traditional, less costly diuretic in preventing death from all causes and, at the same time, is associated with significantly higher risk of adverse coronary or cardiac events including, a 25% higher risk of coronary heart disease and a 100% greater risk of congestive heart failure. Although the place of Cardura in the treatment of hypertension has been

questioned and even cast in doubt, Pfizer continues to promote the drug while aggressively downplaying the ALLHAT findings. The medical community should be aware of the ALLHAT findings so they can evaluate the continued use of Cardura for their patients. Notice to the medical community will allow physicians to familiarize themselves with ALLHAT's findings, to be in a position to respond to patient inquiries and to make any appropriate changes in patient treatment.

The FDA "may also cause to be disseminated information regarding . . . drugs . . . in situations involving, in the opinion of the Secretary, imminent danger to health or gross deception of the consumer." 21 U.S.C. § 375(b). Petitioners therefore request the FDA to issue a press release or "Talk Paper" to give notice to all patients in the United States who have ingested or are ingesting Cardura that ALLHAT has documented an increased risk of heart failure. An enhanced risk of heart failure due to the misinformed use of Cardura as a "first-line" treatment is not tolerable where there are cheaper, more effective treatments or combinations of drugs that may be used and the adverse consequences are potentially critical. Indeed, if the potential adverse consequences were not potentially critical, the NHLBI would not have required that the thousands of Cardura patients participating in ALLHAT immediately discontinue use of the drug. Absent the notice requested, hundreds or thousands of individuals may unwittingly continue hypertension treatment with Cardura based on the erroneous belief that Cardura is as effective or more so than other traditional and less costly drugs. Upon receiving notice, Cardura users will likely consult with their doctors regarding Cardura and change their treatment regimen. Cardura users (and their physicians) need this information to ensure that they are making critical treatment decisions appropriately. Cardura users should be afforded the opportunity to make this

informed choice. The fully-informed medical treatment of patients with hypertension requires notice of the ALLHAT findings to the medical community and users of Cardura.[12]

H. The FDA Should Seek The Input Of Its Cardio-Renal Advisory Committee

In connection with the agency's review of this petition, Petitioners request that the FDA bring the issues raised by the ALLHAT study and the relief requested before the agency's Cardio-Renal Advisory Committee for their review and input, pursuant to 21 C.F.R. §§ 10.60(c)(2) and 10.65. In other instances where serious public health issues have arisen with respect to approved drug products, the FDA has consistently sought the advise of its expert panels. For example, the FDA brought issues regarding the safety and labeling of Rezulin and Accutane before the appropriate advisory committees on March 26, 1999 and September 19, 2000. Such input has been invaluable to the agency in evaluating the "real world" implications of such safety issues. Petitioners request the opportunity to address the committee through their representative medical experts and attorneys.

Should the FDA, however, deny Petitioners' request to bring the ALLHAT issues before the Cardio-Renal Advisory Committee, Petitioners request the opportunity to meet with officials of the agency's Center for Drug Evaluation and Research, including the Division of Cardio-Renal Drug Products, and with experts from the NHLBI and Pfizer in order to present the views of medical experts regarding the imminent danger to patients using Cardura.

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[12] FDA should also require the insertion of a boxed warning on the labeling of Cardura (and to generic doxazosin mesylate tablets) and such additional labeling changes (including changes in the approved indication, warnings, precautions, and contraindications), consistent with the emergency notice, as the agency may deem appropriate.

CERTIFICATION

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

(Signature) Salvatore J. Graziano/lmd

Salvatore J. Graziano

(Name of petitioner) Attorney for Petitioners Lawrence D. Bernhardt and Arnold Liebman

(Mailing address) Milberg Weiss Bershad Hynes & Lerach LLP
One Pennsylvania Plaza, New York, New York 10119

(Telephone number) (212) 594-5300

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OFFICES IN:

SAN DIEGO
SAN FRANCISCO
BOCA RATON
LOS ANGELES
SEATTLE

DIRECT LINE:

January 4, 2001

VIA FACSIMILE

Ms. Jenny Butler
5630 Fishers Lane, Room 1061
Mail Stop HFA-305
Rockville, MD 20852

Re: Citizen Petition of Lawrence D. Bernhardt and Arnold Liebman

Dear Ms. Butler:

In response to your question whether the above-referenced Citizen Petition is fully releasable to the public in light of the attachment of documents marked confidential, please be advised that all of the attached documents were publicly filed in the United States District Court for the Southern District of New York and therefore are fully releasable.

In response to your question regarding the environmental impact study under 21 C.F.R. 10.30, please be advised that such a study is categorically excluded under 21 C.F.R. 25.31.

Sincerely,

Salvatore J. Graziano

COMPENDIUM OF SOURCES FOR CITIZEN PETITION OF LAWRENCE D. BERNHARDT AND ARNOLD LEIBMAN

Dated: January 3, 2000

MILBERG WEISS BERSHAD HYNES & LERACH LLP

Salvatore J. Graziano
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(212) 594-5300

Attorneys for Petitioners

Pfizer Pharmaceuticals Group
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235 East 42nd Street
New York, NY 10017-5755
Tel 212 573 7291 Fax 212 573 1563

Pfizer

Pfizer Pharmaceuticals

Copy 1 - 2110

Rita A. Wittich
Director—Regulatory Affairs

September 30, 1999

Department of Health and Human Services
Food and Drug Administration (HFD-240)
5600 Fishers Lane
Rockville, MD 20857

RE: Cardura (doxazosin mesylate) Tablets
NDA 19-668
21 CFR 314.81 (b)3(i)

Cardura (doxazosin mesylate) Tablets for Benign Prostatic Hyperplasia*
NDA- 20-371
21 CFR 314.81 (b)3(i)

Dear Sir or Madam:

We are submitting the attached advertising and/or promotional labeling at its initial dissemination.

Identification of this material is listed herein.

Hypertension and Diabetes: A Common Combination XC332V99

Sincerely,

Rita A. Wittich /fv

*Cover letter only

CONFIDENTIAL

Note: Form 2253 is required by law. Reports are required for approved NDAs and ANDAs (21 CFR 314.81)

TRANSMITTAL OF ADVERTISEMENTS AND PROMOTIONAL LABELING FOR DRUGS AND BIOLOGICS FOR HUMAN USE

1. DATE SUBMITTED: 9/30/99

2. LABEL REVIEW NO. (Biologics):

Form Approved: OMB No. 0910-0376
Expiration Date: August 31, 2001
See OMB Statement on Reverse or Part I

3. NDA/ANDA/AADA CR BLA/PLA/PMA Number: NDA 19-668

Single product ☐ Multiple products ☒

For multiple products, submit completed form and specimen of advertising/promotional materials to one application of choice, and attach separate sheet addressing items 3-5 for remainder of products. Refer to No. 3 on instruction sheet.

4. PROPRIETARY NAME	5. ESTABLISHED NAME	6. PACKAGE INSERT DATE and ID NO (Latest final printed labeling)	7. MANUFACTURER NAME
Cardura Tablets	doxazosinmesylate Prod. Code No.	6/97 - 69-4538-00-6	License No (Biologics)

FDA/CBER USE ONLY

REVIEWED BY:	DATE	RETURNED BY:	DATE

8. **ADVERTISEMENT / PROMOTIONAL LABELING MATERIALS**

Material Type (use FDA codes) a.	Dissemination/ Publication Date b.	Applicant's Material ID Code and/or description c.	Previous review No. if applicable / date (PLA Submissions) d.	COMMENTS
PSA	10/6/99	XC332V99		

9. TYPED NAME AND TITLE OF RESPONSIBLE OFFICIAL OR AGENT
Rita Wittich, Director, Regulatory Affairs

10. SIGNATURE OF RESPONSIBLE OFFICIAL

11. APPLICANT'S RETURN ADDRESS
Pfizer Inc
Regulatory Affairs
235 East 42nd Street
New York, New York 10017

12. RESPONSIBLE OFFICIAL'S
a. PHONE NO.
(212) 573-7291
b. FAX NO.
(212) 573-1563

13. BIOLOGICAL PRODUCTS: (Check one)
☐ Part I/Draft ☐ Part II/Final

EF

FORM FDA 2253 (8/98) PREVIOUS EDITION IS OBSOLETE.

CONFIDENTIAL

BERNHARDT/PFIZER CDC 3
01 072275

MULTIPLE PRODUCTS

Product(Name)	NDA#:	ID Code	PI Date & Number
Glucotrol XL (glipizide)	20-329	XC332V99	8/99 – 69-4952-00-5

HYPERTENSION AND DIABETES:
a common combination

43 million

43 million Americans have high blood pressure[1]

10 million

Over 10 million Americans have physician-diagnosed diabetes[2]

54%

In one study, the prevalence of hypertension was 54% higher in patients with diabetes than in nondiabetics[3]

4 times greater

Another study showed that mortality rates were 4 times greater for diabetics with high blood pressure[3]

As with all sulfonylureas, hypoglycemia may occur.

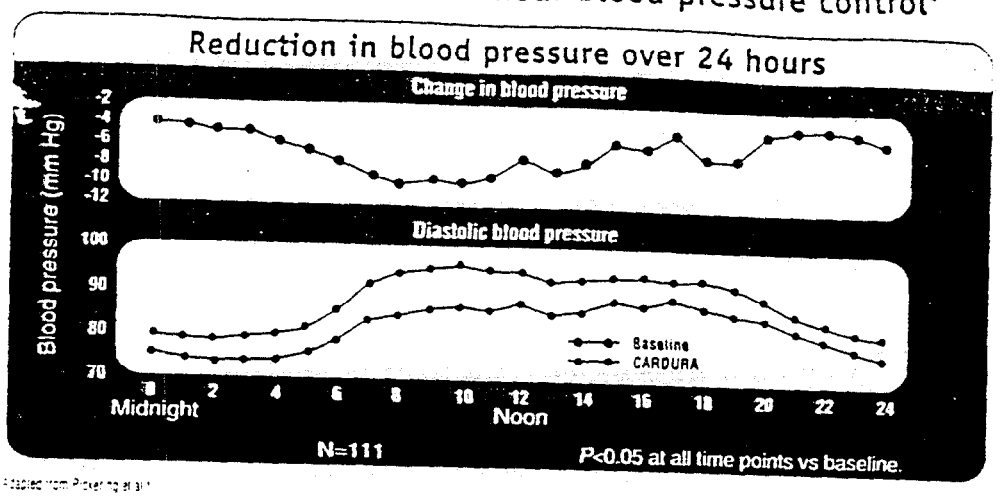
Please see full prescribing information for GLUCOTROL XL and CARDURA on last pages.

ONCE DAILY GLUCOTROL XL (glipizide) extended release tablets

ONCE A-DAY CARDURA (doxazosin mesylate)

Cardura® (doxazosin mesylate) provides effective blood pressure control

Cardura provides effective 24-hour blood pressure control*

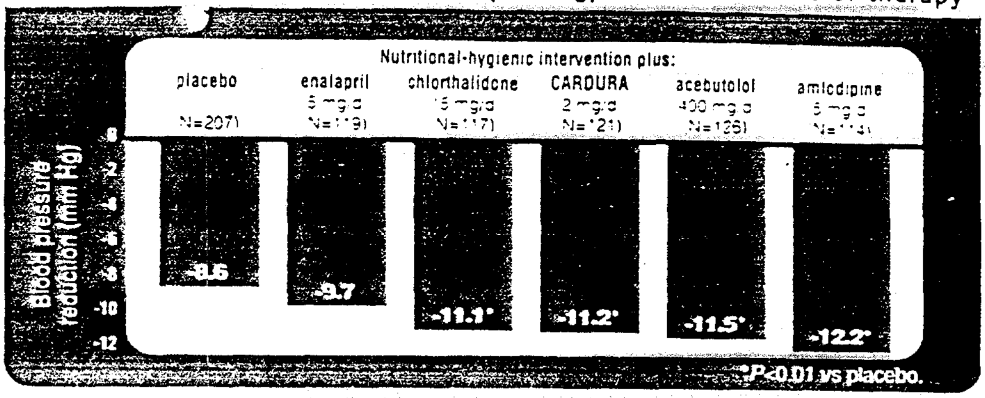


*Adapted from Prisant et al.[1]

The side effects reported significantly more often than placebo in hypertension studies were dizziness, somnolence, and fatigue. These were generally mild and transient. Only 2% of patients discontinued therapy due to adverse effects—the same as with placebo. Syncope has been reported, but rarely (<1%).

Cardura offers comparable efficacy with other major antihypertensive classes[5]

Change in diastolic blood pressure (mm Hg) after 48 months of therapy

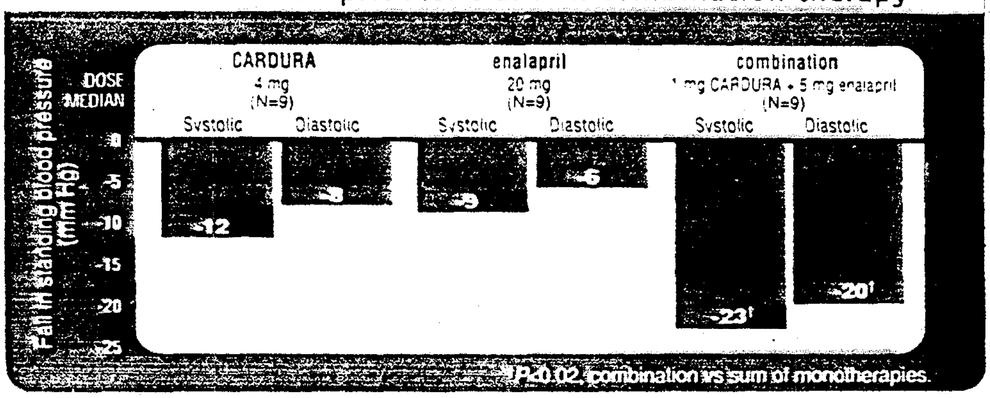


Adapted from Neaton et al.[5]

Adapted from the 48-month results of the Treatment of Mild Hypertension Study (TOMHS), a randomized, double-blind, placebo-controlled trial of a nutritional-hygienic regimen along with various drug therapies. [illegible] ... The chart above represents participants at 48 months.

Cardura is effective in combination to treat difficult-to-control hypertension[6]

Cardura and enalapril alone and in combination therapy



Adapted from Brown and Dickerson.[6]

Results of a double-blind crossover trial of CARDURA and enalapril in 9 patients with essential hypertension (entry diastolic blood pressure between 95 and 120 mm Hg) using 3 consecutive treatment periods of 6 weeks, each consisting of a 2-week placebo run-in and 4 weeks of active treatment. Blood pressure was recorded supine and standing at each visit; the change between the baseline for each period (i.e., at the end of the 2-week placebo run-in) and at the end of the 4-week active treatment. Dose ranging took place in the first 2 weeks of active treatment (1 to 4 mg CARDURA, 5 to 20 mg of enalapril). †P<0.02 combination therapy versus simple addition of single-therapy periods.

Please see full prescribing information for CARDURA on last pages.

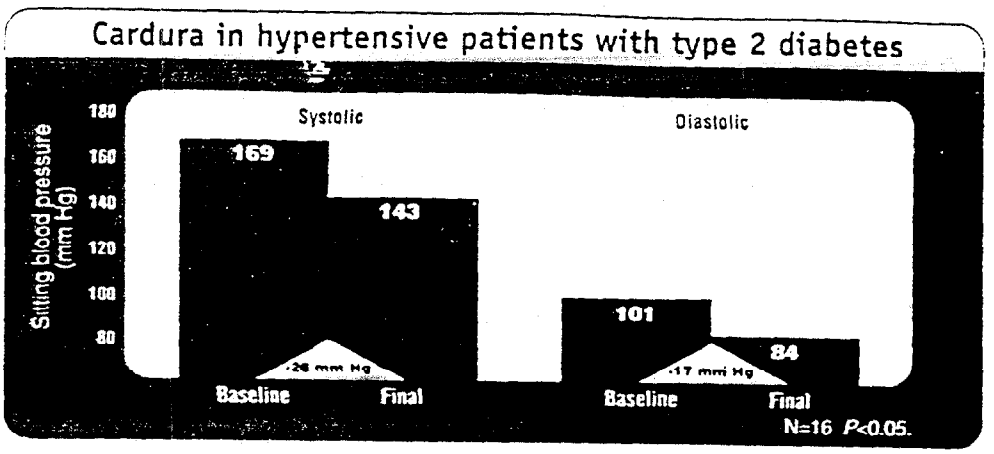
ONCE-A-DAY CARDURA® (doxazosin mesylate)

BERNHARDT PFIZER [illegible]
01 [illegible]

Cardura® (doxazosin mesylate) considers the patient with type 2 diabetes

In patients with diabetes and hypertension

Cardura controls blood pressure in hypertensive patients with type 2 diabetes[7]



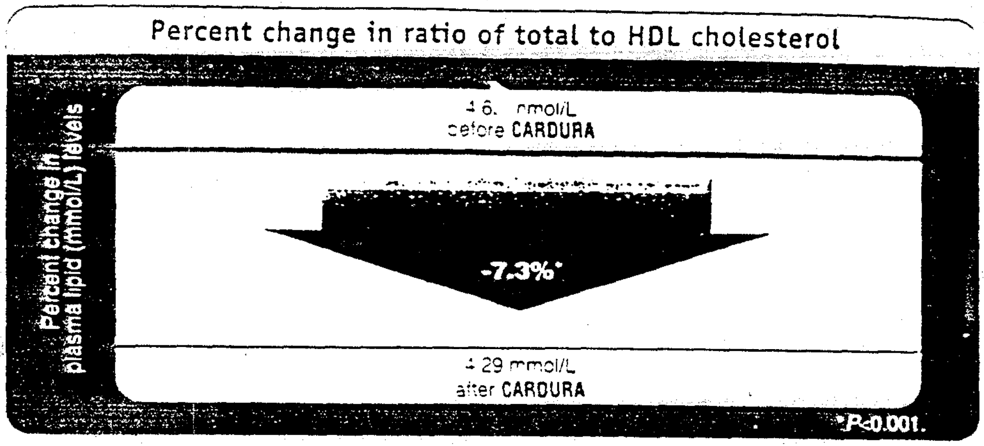
Adapted from Dash grand study.[7]

Results of a 16-week, single-blind treatment of CARDURA in 16 hypertensive patients with concomitant type 2 diabetes. All 16 evaluable patients had the mean blood pressure control, sitting diastolic blood pressure ≤90 mm Hg, with a reduction of ≥5 mm Hg from baseline at a mean dose of 3.6 mg once daily. Statistically significant reductions from mean baseline blood pressure ($P<0.05$) were observed throughout the study period. There were no significant differences in fasting blood glucose levels and in blood lipid profiles between baseline and final visits.

The side effects reported significantly more often than placebo in BPH studies were dizziness/vertigo (15.6%/9.0%), fatigue (8.0%/1.7%), hypotension (1.7%/0.0%), edema (2.7%/0.7%), and dyspnea (2.6%/0.3%). The side effects reported significantly more often than placebo in hypertension studies were dizziness, somnolence, and fatigue. These were generally mild and transient. Only 2% of patients discontinued therapy due to adverse effects—the same as with placebo. Syncope has been reported, but rarely (<1%).

As with all alpha blockers, Cardura can cause marked hypotension with syncope and other postural symptoms, such as dizziness. Blood pressure should be measured after the first dose and with each increase in dose. If Cardura is discontinued for several days, therapy should be restarted using the initial dosing regimen.

Cardura has no adverse effects on the lipid profile[8]

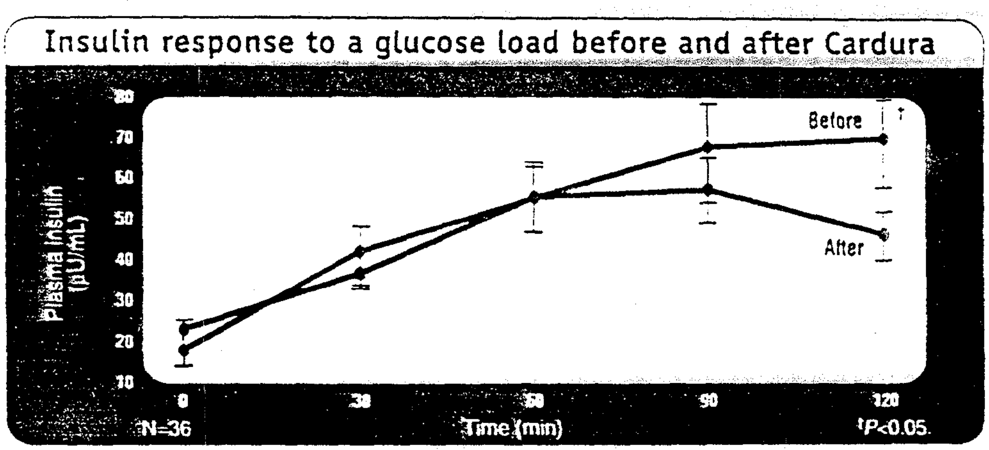


Adapted from Maheux et al.[8]

A 4-month study designed to examine the effect of CARDURA in patients with hypertension. Of the 30 patients in the study, 13 had type 2 diabetes; 17 were nondiabetic. Sixteen of the study participants were undergoing treatment for hypertension. All patients continued their medications and normal exercise/diet regimens throughout the study. After an 8-week washout period, the patients received CARDURA beginning at 1 mg/day and titrated weekly to an optimal daily dosage of 1, 2, 4, 8, or 16 mg. Daily treatment continued at this dosage for the remainder of the study. To determine treatment efficacy, patients underwent weekly blood pressure monitoring and a more thorough evaluation twice during the study period—once after the washout period (baseline measurement) and again after the 10-week maintenance period. For these evaluations, levels of plasma glucose, insulin and other parameters (including lipoproteins) were measured.

THE CLINICAL SIGNIFICANCE OF THIS CHANGE IS UNCERTAIN. Cholesterol is just one parameter to consider when selecting the best individualized therapy for a given patient.

Cardura has no adverse effects on blood insulin levels[9]



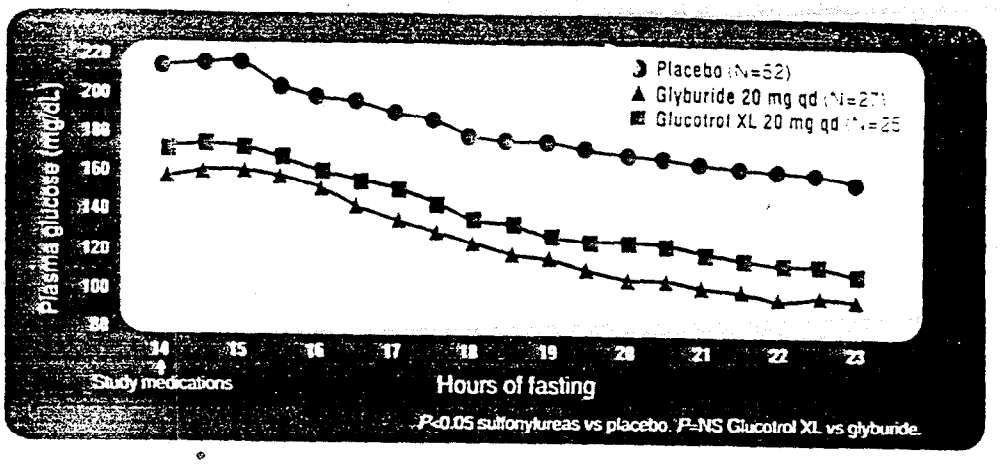
Adapted from Dominguez et al.[9]

The insulin response to a glucose load before and after 8 weeks of CARDURA was examined in 36 type 2 diabetic patients (HbA_{1c} <12%) with mild-to-moderate hypertension (diastolic blood pressure 90 to 105 mm Hg). After an 8-week period of withdrawal of previous antihypertensive treatment, patients began CARDURA at 1 mg/day, and were then titrated at weekly intervals over a maximum of 5 weeks based on their blood pressure response and side effects to a maximum dose of 16 mg/day. CARDURA was then maintained for a minimum of 8 weeks. The mean dose of CARDURA was 7.3 mg/day at the end of the titration phase and 8.0 mg/day at the end of the maintenance phase. Insulin and glucose levels were measured at 0, 30, 60, 90, and 120 minutes after a glucose load (1 g/kg) at the end of the washout and maintenance periods.

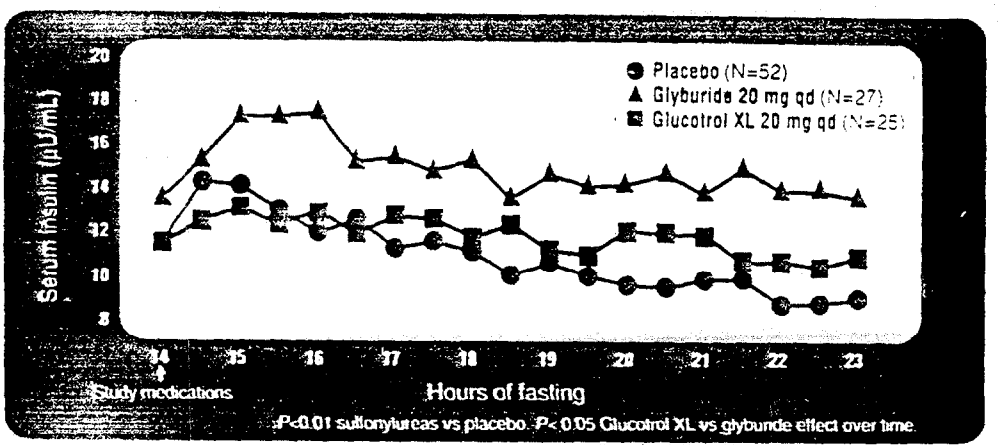
Please see full prescribing information for CARDURA on last pages.

Glucotrol XL® (glipizide) extended-release tablets control blood glucose levels with lower fasting insulin levels than glyburide

Glucotrol XL delivered comparable fasting plasma glucose levels (FPG) vs glyburide[10,11]



Glucotrol XL delivered significantly lower fasting insulin levels vs glyburide[10,11]



The effects on 23-hour fast were compared in a double-blind, placebo-controlled, 3-week randomized study of elderly patients with type 2 diabetes (aged 65 to 75). All patients (N=52) received a placebo pill for 1 week after which patients underwent a 23-hour fast. During the last 9 hours of the fast, half-hourly monitoring of plasma glucose and insulin was performed. Patients were then randomized to receive Glucotrol XL (N=25) or glyburide (N=27). During the second week of the study, patients received either glyburide 10 mg or Glucotrol XL 10 mg. At the end of week 2, the 23-hour fasting and insulin tests were repeated. During the third week of the study, patients received either glyburide 20 mg or Glucotrol XL 20 mg. At the end of week 3, the 23-hour fasting tests were repeated. The above graphs show plasma glucose and insulin values measured during the last 9 hours of the fast at the end of week 3.[10,11]

- No hypoglycemia observed among study participants[10,11]*

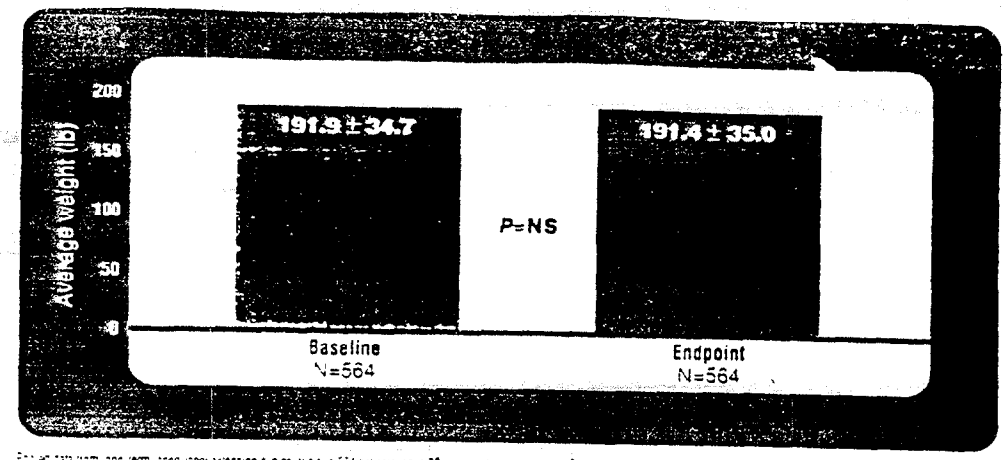
*In this study, hypoglycemia was defined as plasma glucose levels <60 mg/dL plus typical hypoglycemic symptoms or plasma glucose levels <50 mg/dL.[10,11]

As with all sulfonylureas, hypoglycemia may occur.

Please see Glucotrol XL full prescribing information on last pages.

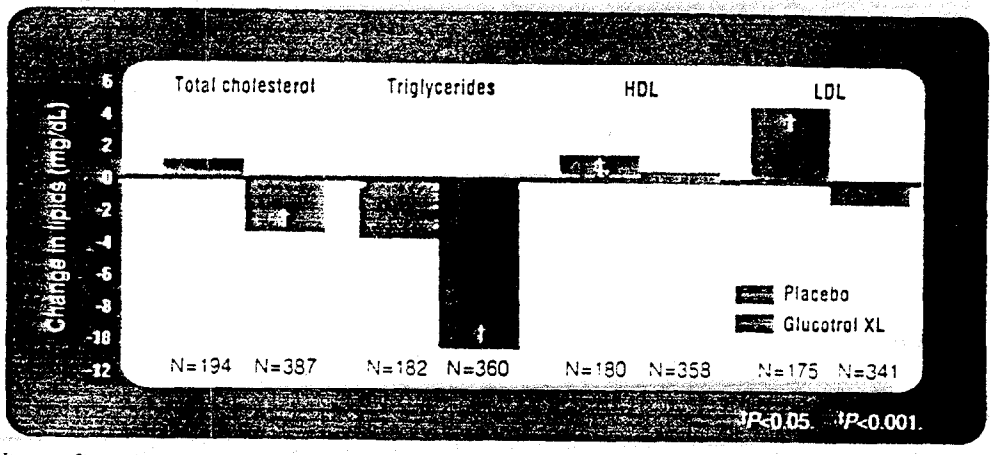
Glucotrol XL had no adverse effect on body weight or lipid levels

Glucotrol XL did not increase body weight in long-term extension studies[10]



Pooled data from long-term open-label extension studies in which 564 patients aged 30 years and older with type 2 diabetes were combined and analyzed to review the clinical experience with Glucotrol XL. The mean body weight comparison in these extension studies patients were titrated over an 8-week period to their optimal level of Glucotrol XL as determined by FPG levels. The recommended starting dose was 5 mg daily, titrated up to a maximum daily dose of 20 mg. Note: The maximum approved daily dose is 40 mg. Once the optimal dose was reached, the patient remained at that dose unless titration to a higher or lower dose was medically indicated. Patients were evaluated weekly until optimal dose was reached; they were then evaluated at 3-month intervals. All 6 months and endpoint. The dose was titrated based on FPG levels. Mean duration of exposure to treatment was 22.7 months, ranging from 9 days to 1.3 months, for 564 patients at endpoint.[10]

Glucotrol XL did not adversely affect the lipid profile[10,12]



The effects of Glucotrol XL on glycemic control, as well as various metabolic parameters, of patients with type 2 diabetes were assessed in a 16-week, multicenter, randomized, double-blind, placebo-controlled, parallel dose-titration study. The study included a 1-week washout phase, a 3-week single-blind placebo phase (baseline), a 4-week double-blind titration phase, and an 8-week double-blind treatment phase (end point) using 5 to 20 mg of Glucotrol XL.[12]

As with all sulfonylureas, hypoglycemia may occur.

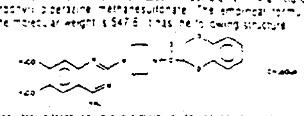
Please see Glucotrol XL full prescribing information on last pages.

ONCE DAILY Glucotrol XL (glipizide) extended release tablets

Cardura®
(doxazosin mesylate)
Tablets

DESCRIPTION

CARDURA® (doxazosin mesylate) is a quinazoline compound that is a selective inhibitor of the $alpha_1$ subtype of alpha adrenergic receptors. The chemical name of doxazosin mesylate is 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(1,4-benzodioxan-2-ylcarbonyl) piperazine methanesulfonate. The empirical formula for doxazosin mesylate is $C_{23}H_{25}N_5O_5 \cdot CH_4O_3S$ and the molecular weight is 547.6. It has the following structure:



CARDURA® (doxazosin mesylate) is freely soluble in dimethylsulfoxide, soluble in dimethylformamide, slightly soluble in methanol, ethanol, and water (0.8% at 25°C), and very slightly soluble in acetone and methylene chloride. CARDURA® is available as colored tablets for oral use and contains 1 mg (white), 2 mg (yellow), 4 mg (orange) and 8 mg (green) of doxazosin as the free base.

The inactive ingredients for all tablets are: microcrystalline cellulose, lactose, sodium starch glycolate, magnesium stearate and sodium lauryl sulfate. The 2 mg tablet contains D & C yellow 10 and FD & C yellow 6; the 4 mg tablet contains FD & C yellow 6; the 8 mg tablet contains FD & C blue 10 and D & C yellow 10.

CLINICAL PHARMACOLOGY

Pharmacodynamics

A. *Benign Prostatic Hyperplasia (BPH)*

Benign prostatic hyperplasia (BPH) is a common cause of urinary outflow obstruction in aging males. Severe BPH may lead to urinary retention and renal damage. A static and a dynamic component contribute to the symptoms and reduced urinary flow rate associated with BPH. The static component is related to an increase in prostate size caused, in part, by a proliferation of smooth muscle cells in the prostatic stroma. However, the severity of BPH symptoms and the degree of urethral obstruction do not correlate well with the size of the prostate. The dynamic component of BPH is associated with an increase in smooth muscle tone in the prostate and bladder neck. The degree of tone in this area is mediated by the $alpha_1$ adrenoceptor, which is present in high density in the prostatic stroma, prostatic capsule and bladder neck. Blockade of the $alpha_1$ receptor decreases urethral resistance and may relieve the obstruction and BPH symptoms. In the human prostate, CARDURA® antagonizes phenylephrine ($alpha_1$ agonist)-induced contractions, in vitro, and binds with high affinity to the $alpha_{1c}$ adrenoceptor. The receptor subtype is thought to be the predominant functional type in the prostate. CARDURA® acts within 1-2 weeks to decrease the severity of BPH symptoms and improve urinary flow rate. Since $alpha_1$ adrenoceptors are of low density in the urinary bladder (apart from the bladder neck), CARDURA® should maintain bladder contractility.

The efficacy of CARDURA® was evaluated extensively in over 900 patients with BPH in double-blind, placebo-controlled trials. CARDURA® treatment was superior to placebo in improving patient symptoms and urinary flow rate. Significant relief with CARDURA® was seen as early as one week into the treatment regimen, with CARDURA® treated patients (N=173) showing a significant (p<0.01) increase in maximum flow rate of 0.8 mL/sec compared to a decrease of 0.5 mL/sec in the placebo group (N=41). In long-term studies improvement was maintained for up to 2 years of treatment in 66-71% of patients. Improvements above baseline were seen in both symptoms and maximum urinary flow rate.

In three placebo-controlled studies of 14-16 weeks duration obstructive symptoms (hesitation, intermittency, dribbling, weak urinary stream, incomplete emptying of the bladder) and irritative symptoms (nocturia, daytime frequency, urgency, burning) of BPH were evaluated at each visit by patient-assessed symptom questionnaires. The bothersomeness of symptoms was measured with a modified Boyarsky questionnaire. Symptom severity/frequency was assessed using a modified Boyarsky questionnaire or an AUA-based questionnaire. Uroflowmetric evaluations were performed at times of peak (2-6 hours post-dose) and/or trough (24 hours post-dose) plasma concentrations of CARDURA®.

The results from the three placebo-controlled studies (N=609) showing significant efficacy with 4 mg and 8 mg doxazosin are summarized in Table 1. In all three studies, CARDURA® resulted in statistically significant relief of obstructive and irritative symptoms compared to placebo. Statistically significant improvements of 2.3-3.3 mL/sec in maximum flow rate were seen with CARDURA® in Studies 1 and 2, compared to 0.1-0.7 mL/sec with placebo.

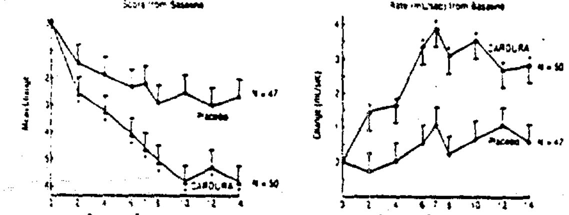
TABLE 1
SUMMARY OF EFFECTIVENESS DATA IN PLACEBO-CONTROLLED TRIALS

	SYMPTOM SCORE[a]			MAXIMUM FLOW RATE (mL/sec)		
	N	MEAN BASELINE	MEAN[b] CHANGE	N	MEAN BASELINE	MEAN[c] CHANGE
STUDY 1 (Titration to maximum dose of 8 mg)[d]						
Placebo	47	15.6	-2.3	41	9.7	+0.7
CARDURA	49	14.5	-4.9**	41	9.8	+2.9**
STUDY 2 (Titration to fixed dose—14 weeks)[d]						
Placebo	37	20.7	-2.5	30	10.6	+0.1
CARDURA 4 mg	38	21.2	-5.3**	32	9.8	+2.3*
CARDURA 8 mg	42	19.9	-4.2*	36	10.5	+3.3**
STUDY 3 (Titration to fixed dose—12 weeks)						
Placebo	47	14.9	-4.7	44	9.9	+1.1
CARDURA 4 mg	46	15.6	-6.1*	46	9.5	+2.6

[a] AUA questionnaire (range 0-30) in studies 1 and 3
Modified Boyarsky Questionnaire (range 0-39) in study 2
[b] Change is to endpoint
[c] Change is to fixed dose efficacy phase (22-25 hours post-dose for studies 1 and 3 and 2-4 hours post dose for study 2
[d] Study in hypertensives with BPH
[e] 25 patients received a dose of 8 mg CARDURA®
*, ** p<0.05, 0.01 compared to placebo mean change.

In one fixed dose study (study 2) CARDURA® (doxazosin mesylate) therapy (4-8 mg, once daily) resulted in a significant and sustained improvement in maximum urinary flow rate of 2.3-3.3 mL/sec (Table 1) compared to placebo (0.1 mL/sec). In this study, the only study in which weekly evaluations were made, significant improvement with CARDURA® vs. placebo was seen after one week. The proportion of patients who responded with a maximum flow rate improvement of ≥3 mL/sec was significantly larger with CARDURA® (34-42%) than placebo (13-17%). A significantly greater improvement was also seen in average flow rate with CARDURA® (1.6 mL/sec) than with placebo (0.2 mL/sec). The onset and time course of symptom relief and increased urinary flow from study 1 are illustrated in Figure 1.

Figure 1—Study 1



† p < 0.05 Compared to Placebo   • p < 0.05 Compared to Baseline   Doxazosin Titration to Maximum of 8 mg

In BPH patients (N=450) treated for up to 2 years in open-label studies, CARDURA® therapy resulted in significant improvement above baseline in urinary flow rates and BPH symptoms. The significant effects of CARDURA® were maintained over the entire treatment period.

Although blockade of $alpha_1$ adrenoceptors also lowers blood pressure in hypertensive patients with increased peripheral vascular resistance, CARDURA® treatment of normotensive men with BPH did not result in a clinically significant blood pressure lowering effect (Table 2). The proportion of normotensive patients with a sitting systolic blood pressure less than 90 mmHg and/or diastolic blood pressure less than 60 mmHg at any time during treatment with CARDURA® 1-8 mg once daily was 6.7% with doxazosin and not significantly different (statistically) from that with placebo (5%).

CLINICAL PHARMACOLOGY (continued)

TABLE 2
Mean Changes in Blood Pressure from Baseline to the Mean of the Final Efficacy Phase in Normotensives (Diastolic BP <90 mmHg) in Two Double-blind, Placebo-controlled U.S. Studies with CARDURA® 1-8 mg once daily

	Placebo (N=85)		CARDURA® (N=183)	
Sitting BP (mmHg)	**Baseline**	**Change**	**Baseline**	**Change**
Systolic	128.4	-1.4	128.8	-4.9*
Diastolic	79.2	-1.2	79.6	-2.4*
Standing BP (mmHg)	**Baseline**	**Change**	**Baseline**	**Change**
Systolic	128.5	-0.3	128.5	-5.3*
Diastolic	80.5	-0.7	80.4	-2.6*

*p≤0.05 compared to placebo

B. *Hypertension*

The mechanism of action of CARDURA® (doxazosin mesylate) is selective blockade of the $alpha_1$ (postjunctional) subtype of adrenergic receptors. Studies in normal human subjects have shown that doxazosin competitively antagonized the pressor effects of phenylephrine (an $alpha_1$ agonist) and the systolic pressor effect of norepinephrine. Doxazosin and prazosin have similar abilities to antagonize phenylephrine. The antihypertensive effect of CARDURA® results from a decrease in systemic vascular resistance. The parent compound doxazosin is primarily responsible for the antihypertensive activity. The low plasma concentrations of known active and inactive metabolites of doxazosin (2-piperazinyl, 6'- and 7'-hydroxy and 6- and 7-O-desmethyl compounds) compared to parent drug indicate that the contribution of even the most potent compound (6'-hydroxy) to the antihypertensive effect of doxazosin in man is probably small. The 6'- and 7'-hydroxy metabolites have demonstrated antioxidant properties at concentrations of 5 μM, in vitro.

Administration of CARDURA® results in a reduction in systemic vascular resistance. In patients with hypertension there is little change in cardiac output. Maximum reductions in blood pressure usually occur 2-6 hours after dosing and are associated with a small increase in standing heart rate. Like other $alpha_1$-adrenergic blocking agents, doxazosin has a greater effect on blood pressure and heart rate in the standing position.

In a pooled analysis of placebo-controlled hypertension studies with about 300 hypertensive patients per treatment group, doxazosin, at doses of 1-16 mg given once daily, lowered blood pressure at 24 hours by about 10/8 mmHg compared to placebo in the standing position and about 9/5 mmHg in the supine position. Peak blood pressure effects (1-6 hours) were larger by about 50-75% (i.e., trough values were about 55-70% of peak effect), with the larger peak-trough differences seen in systolic pressures. There was no apparent difference in the blood pressure response of Caucasians and blacks or of patients above and below age 65. In these predominantly normocholesterolemic patients doxazosin produced small reductions in total serum cholesterol (2-3%), LDL cholesterol (4%), and a similarly small increase in HDL/total cholesterol ratio (4%). The clinical significance of these findings is uncertain. In the same patient population, patients receiving CARDURA® gained a mean of 0.6 kg compared to a mean loss of 0.1 kg for placebo patients.

Pharmacokinetics

After oral administration of therapeutic doses, peak plasma levels of CARDURA® (doxazosin mesylate) occur at about 2-3 hours. Bioavailability is approximately 65%, reflecting first pass metabolism of doxazosin by the liver. The effect of food on the pharmacokinetics of CARDURA® was examined in a crossover study with twelve hypertensive subjects. Reductions of 18% in mean maximum plasma concentration and 12% in the area under the concentration-time curve occurred when CARDURA® was administered with food. Neither of these differences was statistically or clinically significant.

CARDURA® is extensively metabolized in the liver, mainly by O-demethylation of the quinazoline nucleus or hydroxylation of the benzodioxan moiety. Although several active metabolites of doxazosin have been identified, the pharmacokinetics of these metabolites have not been characterized. In a study of two subjects administered radiolabelled doxazosin 2 mg orally and 1 mg intravenously on two separate occasions, approximately 63% of the dose was eliminated in the feces and 9% of the dose was found in the urine. On average only 4.8% of the dose was excreted as unchanged drug in the feces and only a trace of the total radioactivity in the urine was attributed to unchanged drug. At the plasma concentrations achieved by therapeutic doses approximately 98% of the circulating drug is bound to plasma proteins.

Plasma elimination of doxazosin is biphasic, with a terminal elimination half-life of about 22 hours. Steady-state studies in hypertensive patients given doxazosin doses of 2-16 mg once daily showed linear kinetics and dose proportionality. In two studies, following the administration of 2 mg orally once daily, the mean accumulation ratios (steady-state AUC vs. first dose AUC) were 1.2 and 1.7. Enterohepatic recycling is suggested by secondary peaking of plasma doxazosin concentrations.

In a crossover study in 24 normotensive subjects, the pharmacokinetics and safety of doxazosin were shown to be similar with morning and evening dosing regimens. The area under the curve after morning dosing was, however, 11% less than that after evening dosing and the time to peak concentration after evening dosing occurred significantly later than that after morning dosing (5.6 hr vs. 3.5 hr).

The pharmacokinetics of CARDURA® (doxazosin mesylate) in young (<65 years) and elderly (≥65 years) subjects were similar for plasma half-life values and oral clearance. Pharmacokinetic studies in elderly patients and patients with renal impairment have shown no significant alterations compared to younger patients with normal renal function. Administration of a single 2 mg dose to patients with cirrhosis (Child-Pugh Class A) showed a 40% increase in exposure to doxazosin. There are only limited data on the effects of drugs known to influence the hepatic metabolism of doxazosin (e.g., cimetidine (see PRECAUTIONS)). As with any drug wholly metabolized by the liver, use of CARDURA® in patients with altered liver function should be undertaken with caution.

In two placebo-controlled studies, of normotensive and hypertensive BPH patients, in which doxazosin was administered in the morning and the titration interval was two weeks and one week, respectively, trough plasma concentrations of CARDURA® were similar in the two populations. Linear kinetics and dose proportionality were observed.

INDICATIONS AND USAGE

A. *Benign Prostatic Hyperplasia (BPH).* CARDURA® is indicated for the treatment of both the urinary outflow obstruction and obstructive and irritative symptoms associated with BPH: obstructive symptoms (hesitation, intermittency, dribbling, weak urinary stream, incomplete emptying of the bladder) and irritative symptoms (nocturia, daytime frequency, urgency, burning). CARDURA® may be used in all BPH patients whether hypertensive or normotensive. In patients with hypertension and BPH, both conditions were effectively treated with CARDURA® monotherapy. CARDURA® provides rapid improvement in symptoms and urinary flow rate in 66-71% of patients. Sustained improvements with CARDURA® were seen in patients treated for up to 14 weeks in double-blind studies and up to 2 years in open-label studies.

B. *Hypertension.* CARDURA® (doxazosin mesylate) is also indicated for the treatment of hypertension. CARDURA® may be used alone or in combination with diuretics, beta-adrenergic blocking agents, calcium channel blockers or angiotensin-converting enzyme inhibitors.

CONTRAINDICATIONS

CARDURA® is contraindicated in patients with a known sensitivity to quinazolines (e.g., prazosin, terazosin).

WARNINGS

Syncope and "First-dose" Effect: Doxazosin, like other alpha-adrenergic blocking agents, can cause marked hypotension, especially in the upright position, with syncope and other postural symptoms such as dizziness. Marked orthostatic effects are most common with the first dose but can also occur when there is a dosage increase, or if therapy is interrupted for more than a few days. To decrease the likelihood of excessive hypotension and syncope, it is essential that treatment be initiated with the 1 mg dose. The 2, 4, and 8 mg tablets are not for initial therapy. Dosage should then be adjusted slowly (see DOSAGE AND ADMINISTRATION section) with evaluations and increases in dose every two weeks to the recommended dose. Additional antihypertensive agents should be added with caution.

Patients being titrated with doxazosin should be cautioned to avoid situations where injury could result should syncope occur, during both the day and night.

In an early investigational study of the safety and tolerance of increasing daily doses of doxazosin in normotensives beginning at 1 mg/day, only 2 of 6 subjects could tolerate more than 2 mg/day without experiencing symptomatic postural hypotension. In another study of 24 healthy normotensive male subjects receiving initial doses of 2 mg/day of doxazosin, seven (29%) of the subjects experienced symptomatic postural hypotension between 0.5 and 6 hours after the first dose necessitating termination of the study. In this study, 2 of the normotensive subjects experienced syncope. Subsequent trials in hypertensive patients always began doxazosin dosing at 1 mg/day resulting in a 4% incidence of postural side effects at 1 mg/day with no cases of syncope.

In multiple dose clinical trials in hypertension involving over 1500 hypertensive patients with dose titration every one to two weeks, syncope was reported in 0.7% of patients. None of these events occurred at the starting dose of 1 mg and 1.2% (8/664) occurred at 16 mg/day.

In placebo-controlled, clinical trials in BPH, 3 out of 665 patients (0.5%) taking doxazosin reported syncope. Two of the patients were taking 1 mg doxazosin, while one patient was taking 2 mg doxazosin when syncope occurred. In the open-label, long-term extension follow-up of approximately 450 BPH patients, there were 3 reports of syncope (0.7%). One patient was taking 2 mg, one patient was taking 8 mg and one patient was taking 12 mg when syncope occurred. In a clinical pharmacology study, one subject receiving 2 mg experienced syncope.

If syncope occurs, the patient should be placed in a recumbent position and treated supportively as necessary.

Priapism: Rarely (probably less frequently than once in every several thousand patients), $alpha_1$ antagonists such as doxazosin have been associated with priapism (painful penile erection, sustained for hours and unrelieved by sexual intercourse or masturbation). Because this condition can lead to permanent impotence if not promptly treated, patients must be advised about the seriousness of the condition (see **PRECAUTIONS: Information for Patients**).

PRECAUTIONS

General:

Prostate Cancer: Carcinoma of the prostate causes many of the symptoms associated with BPH and the two disorders frequently co-exist. Carcinoma of the prostate should therefore be ruled out prior to commencing therapy with CARDURA®.

Orthostatic Hypotension: While syncope is the most severe orthostatic effect of CARDURA®, other symptoms of lowered blood pressure, such as dizziness, lightheadedness, or vertigo can occur, especially at initiation of therapy or at the time of dose increases.

a) Hypertension

These symptoms were common in clinical trials in hypertension, occurring in up to 23% of all patients treated and causing discontinuation of therapy in about 2%.

In placebo-controlled titration trials in hypertension, orthostatic effects were minimized by beginning therapy at 1 mg per day and titrating every two weeks to 2, 4, or 8 mg per day. There was an increased frequency of orthostatic effects in patients given 8 mg or more, 10%, compared to 5% at 1-4 mg and 3% in the placebo group.

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PRECAUTIONS (continued)

In Benign Prostatic Hyperplasia

In placebo-controlled trials in BPH, the incidence of orthostatic hypotension with doxazosin was 0.3% and did not increase with increasing dosage (to 8 mg/day). The incidence of discontinuations due to hypotensive or orthostatic symptoms was 3.3% with doxazosin and 1% with placebo. The titration interval in these studies was one to two weeks.

Patients in occupations in which orthostatic hypotension could be dangerous should be treated with particular caution. As alpha₁ antagonists can cause orthostatic effects, it is important to evaluate standing blood pressure two minutes after standing and patients should be advised to exercise care when arising from a supine or sitting position.

If hypotension occurs, the patient should be placed in the supine position and, if this measure is inadequate, volume expansion with intravenous fluids or vasopressor therapy may be used. A transient hypotensive response is not a contraindication to further doses of CARDURA® (doxazosin mesylate).

Information for Patients (See Patient Package Insert): Patients should be made aware of the possibility of syncopal and orthostatic symptoms, especially at the initiation of therapy, and urged to avoid driving or hazardous tasks for 24 hours after the first dose, after a dosage increase, and after interruption of therapy when treatment is resumed. They should be cautioned to avoid situations where injury could result should syncope occur during initiation of doxazosin therapy. They should also be advised of the need to sit or lie down when symptoms of lowered blood pressure occur, although these symptoms are not always orthostatic, and to be careful when rising from a sitting or lying position. If dizziness, lightheadedness, or palpitations are bothersome they should be reported to the physician, so that dose adjustment can be considered. Patients should also be told that drowsiness or somnolence can occur with CARDURA® (doxazosin mesylate) or any selective alpha₁ adrenoceptor antagonist, requiring caution in people who must drive or operate heavy machinery.

Patients should be advised about the possibility of priapism as a result of treatment with alpha₁ antagonists. Patients should know that this adverse event is very rare. If they experience priapism, it should be brought to immediate medical attention for if not treated promptly it can lead to permanent erectile dysfunction (impotence).

Drug/Laboratory Test Interactions: CARDURA® does not affect the plasma concentration of prostate specific antigen in patients treated for up to 3 years. Both doxazosin, an alpha₁ inhibitor, and finasteride, a 5-alpha reductase inhibitor, are highly protein bound and hepatically metabolized. There is no definitive controlled clinical experience on the concomitant use of alpha₁ inhibitors and 5-alpha reductase inhibitors at this time.

Impaired Liver Function: CARDURA® should be administered with caution to patients with evidence of impaired hepatic function or to patients receiving drugs known to influence hepatic metabolism (see CLINICAL PHARMACOLOGY).

Leukopenia/Neutropenia: Analysis of hematologic data from hypertensive patients receiving CARDURA® in controlled hypertension clinical trials showed that the mean WBC (N=474) and mean neutrophil counts (N=419) were decreased by 2.4% and 1.0% respectively, compared to placebo, a phenomenon seen with other alpha blocking drugs. In BPH patients the incidence of clinically significant WBC abnormalities was 0.4% (2/459) with CARDURA® and 0% (0/147) with placebo, with no statistically significant difference between the two treatment groups. A search through a data base of 2400 hypertensive patients and 665 BPH patients revealed 4 hypertensives in which drug-related neutropenia could not be ruled out and one BPH patient in which drug related leukopenia could not be ruled out. Two hypertensives had a single low value on the last day of treatment. Two hypertensives had stable, non-progressive neutrophil counts in the 1000/mm³ range over periods of 20 and 40 weeks. One BPH patient had a decrease from a WBC count of 4800/mm³ to 2700/mm³ at the end of the study; there was no evidence of clinical impairment. In cases where follow-up was available the WBCs and neutrophil counts returned to normal after discontinuation of CARDURA®. No patients became symptomatic as a result of the low WBC or neutrophil counts.

Drug Interactions: Most (98%) of plasma doxazosin is protein bound. In vitro data in human plasma indicate that CARDURA® has no effect on protein binding of digoxin, warfarin, phenytoin or indomethacin. There is no information on the effect of other highly plasma protein bound drugs on doxazosin binding. CARDURA® has been administered without any evidence of an adverse drug interaction to patients receiving thiazide diuretics, beta-blocking agents, and nonsteroidal anti-inflammatory drugs. In a placebo-controlled trial in normal volunteers, the administration of a single 1 mg dose of doxazosin on day 1 of a four-day regimen of oral cimetidine (400 mg twice daily) resulted in a 10% increase in mean AUC of doxazosin (p=0.006), and a slight but not statistically significant increase in mean C_{max} and mean half-life of doxazosin. The clinical significance of this increase in doxazosin AUC is unknown.

In clinical trials, CARDURA® tablets have been administered to patients on a variety of concomitant medications; while no formal interaction studies have been conducted, no interactions were observed. CARDURA® tablets have been used with the following drugs or drug classes: 1) analgesic/anti-inflammatory (e.g., acetaminophen, aspirin, codeine and codeine combinations, ibuprofen, indomethacin); 2) antibiotics (e.g., erythromycin, trimethoprim and sulfamethoxazole, amoxicillin); 3) antihistamines (e.g., chlorpheniramine); 4) cardiovascular agents (e.g., atenolol, hydrochlorothiazide, propranolol); 5) corticosteroids; 6) gastrointestinal agents (e.g., antacids); 7) hypoglycemics and endocrine drugs; 8) sedatives and tranquilizers (e.g., diazepam); 9) cold and flu remedies.

Cardiac Toxicity in Animals: An increased incidence of myocardial necrosis or fibrosis was displayed by Sprague-Dawley rats after 6 months of dietary administration at concentrations calculated to provide 80 mg doxazosin/kg/day and after 12 months of dietary administration at concentrations calculated to provide 40 mg doxazosin/kg/day (AUC exposure in rats 8 times the human AUC exposure with a 12 mg/day therapeutic dose). Myocardial fibrosis was observed in both rats and mice treated in the same manner with 40 mg doxazosin/kg/day for 18 months (exposure 8 times human AUC exposure in rats and somewhat equivalent to human C_{max} exposure in mice). No cardiotoxicity was observed at lower doses (up to 10 or 20 mg/kg/day, depending on the study) in either species. These lesions were not observed after 12 months of oral dosing in dogs at maximum doses of 20 mg/kg/day (maximum plasma concentrations (C_{max}) in dogs 14 times the C_{max} exposure in humans receiving a 12 mg/day therapeutic dose) and in Wistar rats at doses of 100 mg/kg/day (C_{max} exposures 15 times human C_{max} exposure with a 12 mg/day therapeutic dose). There is no evidence that similar lesions occur in humans.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Chronic dietary administration (up to 24 months) of doxazosin mesylate at maximally tolerated doses of 40 mg/kg/day in rats and 120 mg/kg/day in mice revealed no evidence of carcinogenic potential. The highest doses evaluated in the rat and mouse studies are associated with AUCs (a measure of systemic exposure) that are 8 times and 4 times, respectively, the human AUC at a dose of 16 mg/day.

Mutagenicity studies revealed no drug- or metabolite-related effects at either chromosomal or subchromosomal levels.

Studies in rats showed reduced fertility in males treated with doxazosin at oral doses of 20 (but not 5 or 10) mg/kg/day, about 4 times the AUC exposures obtained with a 12 mg/day human dose. This effect was reversible within two weeks of drug withdrawal. There have been no reports of any effects of doxazosin on male fertility in humans.

Pregnancy: Teratogenic Effects, Pregnancy Category C. Studies in pregnant rabbits and rats at daily oral doses of up to 41 and 20 mg/kg, respectively (plasma drug concentrations 10 and 4 times human C_{max} and AUC exposures with a 12 mg/day therapeutic dose), have revealed no evidence of harm to the fetus. A dosage regimen of 82 mg/kg/day in the rabbit was associated with reduced fetal survival. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, CARDURA® should be used during pregnancy only if clearly needed.

Radioactivity was found to cross the placenta following oral administration of labelled doxazosin to pregnant rats.

Nonteratogenic Effects. In peri-postnatal studies in rats, postnatal development at maternal doses of 40 or 50 mg/kg/day of doxazosin (8 times human AUC exposure with a 12 mg/day therapeutic dose) was delayed as evidenced by slower body weight gain and a slightly later appearance of anatomical features and reflexes.

Nursing Mothers: Studies in lactating rats given a single oral dose of 1 mg/kg of [2-¹⁴C]-CARDURA® indicate that doxazosin accumulates in rat breast milk with a maximum concentration about 20 times greater than the maternal plasma concentration. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when CARDURA® is administered to a nursing mother.

Pediatric Use: The safety and effectiveness of CARDURA® as an antihypertensive agent have not been established in children.

Use in Elderly: The safety and effectiveness profile of CARDURA® in BPH was similar in the elderly (age ≥65 years) and younger (age <65 years) patients.

ADVERSE REACTIONS

A. Benign Prostatic Hyperplasia

The incidence of adverse events has been ascertained from worldwide clinical trials in 965 BPH patients. The incidence rates presented below (Table 3) are based on combined data from seven placebo-controlled trials involving once daily administration of CARDURA® (doxazosin mesylate) in doses of 1-16 mg in hypertensives and 0.5-8 mg in normotensives. The adverse events when the incidence in the CARDURA® group was at least 1% are summarized in Table 3. No significant difference in the incidence of adverse events compared to placebo was seen except for dizziness, fatigue, hypotension, edema and dyspnea. Dizziness and dyspnea appeared to be dose-related.

TABLE 3
ADVERSE REACTIONS DURING
PLACEBO-CONTROLLED STUDIES
BENIGN PROSTATIC HYPERPLASIA*

Body System	CARDURA® (N=665)	PLACEBO (N=300)
BODY AS A WHOLE		
Back pain	1.8%	2.0%
Chest pain	1.2%	0.7%
Fatigue	8.0%*	1.7%
Headache	9.9%	9.0%
Influenza-like symptoms	1.1%	1.0%
Pain	2.0%	1.3%
CARDIOVASCULAR SYSTEM		
Hypotension	1.7%*	0.0%
Palpitation	1.2%	0.3%
DIGESTIVE SYSTEM		
Abdominal Pain	2.4%	2.0%
Diarrhea	2.3%	2.0%
Dyspepsia	1.7%	1.7%
Nausea	1.5%	0.7%
METABOLIC AND NUTRITIONAL DISORDERS		
Edema	2.7%*	0.7%
NERVOUS SYSTEM		
Dizziness†	15.6%*	9.0%
Mouth Dry	1.4%	0.3%
Somnolence	3.0%	1.0%
RESPIRATORY SYSTEM		
Dyspnea	2.6%*	0.3%
Respiratory Disorder	1.1%	0.7%
SPECIAL SENSES		
Vision Abnormal	1.4%	0.7%
UROGENITAL SYSTEM		
Impotence	1.1%	1.0%
Urinary Tract Infection	1.4%	2.3%
SKIN & APPENDAGES		
Sweating Increased	1.1%	1.0%
PSYCHIATRIC DISORDERS		
Anxiety	1.1%	0.3%
Insomnia	1.2%	0.3%

*p≤0.05 for treatment differences
†Includes vertigo

In these placebo-controlled studies of 665 CARDURA® patients, treated for a mean of 85 days, additional adverse reactions have been reported. These are less than 1% and not distinguishable from those that occurred in the placebo group. Adverse reactions with an incidence of less than 1% but of clinical interest are (CARDURA® vs. placebo): *Cardiovascular System*: angina pectoris (0.6% vs. 0.7%), postural hypotension (0.3% vs. 0.3%), syncope (0.5% vs. 0.0%), tachycardia (0.9% vs. 0.0%); *Urogenital System*: dysuria (0.5% vs. 1.3%); and *Psychiatric Disorders*: libido decreased (0.8% vs. 0.3%). The safety profile in patients treated for up to three years was similar to that in the placebo-controlled studies.

The majority of adverse experiences with CARDURA® were mild.

B. Hypertension

CARDURA® has been administered to approximately 4000 hypertensive patients [illegible] clinical development program. In that program, minor adverse effects were frequent, [illegible] of patients. In placebo-controlled studies adverse effects occurred in 49% and [illegible] groups, respectively, and led to discontinuation in 2% of patients in each group. The major [illegible] effects (2%), edema, malaise/fatigue, and some heart rate disturbance, each about 2%.

In controlled hypertension clinical trials directly comparing CARDURA® to placebo there was [illegible] dence of side effects, except for dizziness (including postural), weight gain, somnolence and fatigue/malaise. [illegible] edema appeared to be dose related. The prevalence rates presented below are based on [illegible] studies involving once daily administration of doxazosin at doses ranging from 1 to 16 mg. [illegible] reactions, possibly probably related, reported for patients in these hypertension studies where the [illegible] group was at least 0.5% or where the reaction is of particular interest.

TABLE 4
ADVERSE REACTIONS DURING
PLACEBO-CONTROLLED STUDIES

	HYPERTENSION: DOXAZOSIN (N=339)	HYPERTENSION: PLACEBO (N=336)
CARDIOVASCULAR SYSTEM		
Dizziness	19%	9%
Vertigo	2%	1%
Postural Hypotension	0.3%	0%
Edema	4%	3%
Palpitation	2%	3%
Arrhythmia	1%	0%
Hypotension	1%	0%
Tachycardia	0.3%	1%
Peripheral Ischemia	0.3%	0%
SKIN & APPENDAGES		
Rash	1%	1%
Pruritus	1%	1%
MUSCULOSKELETAL SYSTEM		
Arthralgia/Arthritis	1%	0%
Muscle Weakness	1%	0%
Myalgia	1%	0%
CENTRAL & PERIPHERAL N.S.		
Headache	14%	16%
Paresthesia	1%	1%
Kinetic Disorders	1%	0%
Ataxia	1%	0%
Hypertonia	1%	0%
Muscle Cramps	1%	0%
AUTONOMIC		
Mouth Dry	2%	2%
Flushing	1%	0%
SPECIAL SENSES		
Vision Abnormal	2%	1%
Conjunctivitis/Eye Pain	1%	1%
Tinnitus	1%	0.3%

	HYPERTENSION: DOXAZOSIN	HYPERTENSION: PLACEBO
PSYCHIATRIC		
Somnolence	[illegible]	[illegible]
Nervousness	[illegible]	[illegible]
Depression	[illegible]	[illegible]
Insomnia	[illegible]	[illegible]
Sexual Dysfunction	[illegible]	[illegible]
GASTROINTESTINAL		
Nausea	[illegible]	[illegible]
Diarrhea	[illegible]	[illegible]
Constipation	[illegible]	[illegible]
Dyspepsia	[illegible]	[illegible]
Flatulence	[illegible]	[illegible]
Abdominal Pain	[illegible]	[illegible]
Vomiting	[illegible]	[illegible]
RESPIRATORY		
Rhinitis	[illegible]	[illegible]
Dyspnea	[illegible]	[illegible]
Epistaxis	[illegible]	[illegible]
URINARY		
Polyuria	[illegible]	[illegible]
Urinary Incontinence	[illegible]	[illegible]
Micturition Frequency	[illegible]	[illegible]
GENERAL		
Fatigue/Malaise	[illegible]	[illegible]
Chest Pain	[illegible]	[illegible]
Asthenia	[illegible]	[illegible]
Face Edema	[illegible]	[illegible]
Pain	[illegible]	[illegible]

Additional adverse reactions have been reported, but these are, in general, not distinguishable from symptoms that might have occurred in the absence of exposure to doxazosin. The following adverse reactions occurred with a frequency of between 0.5% and 1%: syncope, hypoesthesia, increased sweating, agitation, increased weight. The following additional adverse reactions were reported by <0.5% of 3960 patients who received doxazosin in controlled or open, short- or long-term clinical studies, including international studies. *Cardiovascular System*: angina pectoris, myocardial infarction, cerebrovascular accident; *Autonomic Nervous System*: pallor; *Metabolic*: thirst, gout, hypokalemia; *Hematopoietic*: lymphadenopathy, purpura; *Reproductive System*: breast pain; *Skin Disorders*: alopecia, dry skin, eczema; *Central Nervous System*: paresis, tremor, twitching, confusion, migraine, impaired concentration; *Psychiatric*: paroniria, amnesia, emotional lability, abnormal thinking, depersonalization; *Special Senses*: parosmia, earache, taste perversion, photophobia, abnormal lacrimation; *Gastrointestinal System*: increased appetite, anorexia, fecal incontinence, gastroenteritis; *Respiratory System*: bronchospasm, sinusitis, coughing, pharyngitis; *Urinary System*: renal calculus; *General Body System*: hot flushes, back pain, infection, fever/rigors, decreased weight, influenza-like symptoms.

CARDURA® has not been associated with any clinically significant changes in routine biochemical tests. No clinically relevant adverse effects were noted on serum potassium, serum glucose, uric acid, blood urea nitrogen, creatinine or liver function tests. CARDURA® has been associated with decreases in white blood cell counts (see PRECAUTIONS).

OVERDOSAGE

Experience with CARDURA® overdosage is limited. Two adolescents who each intentionally ingested 40 mg CARDURA® with diclofenac or paracetamol, were treated with gastric lavage with activated charcoal and made full recoveries. A two-year-old child who accidently ingested 4 mg CARDURA® was treated with gastric lavage and remained normotensive during the five-hour emergency room observation period. A six-month-old child accidentally received a crushed 1 mg tablet of CARDURA® and was reported to have been drowsy. A 32-year-old female with chronic renal failure, epilepsy and depression intentionally ingested 60 mg CARDURA® (blood level 0.9 mg/mL; normal values in hypertensives=0.02 mg/mL); death was attributed to a grand mal seizure resulting from hypotension. A 39-year-old female who ingested 70 mg CARDURA®, alcohol and Dalmane® (flurazepam) developed hypotension which responded to fluid therapy.

The oral LD_{50} of doxazosin is greater than 1000 mg/kg in mice and rats. The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of fluid. As doxazosin is highly protein bound, dialysis would not be indicated.

DOSAGE AND ADMINISTRATION

DOSAGE MUST BE INDIVIDUALIZED. The initial dosage of CARDURA® in patients with hypertension and/or BPH is 1 mg given once daily in the a.m. or p.m. This starting dose is intended to minimize the frequency of postural hypotension and first dose syncope associated with CARDURA®. Postural effects are most likely to occur between 2 and 6 hours after a dose. Therefore blood pressure measurements should be taken during this time period after the first dose and with each increase in dose. If CARDURA® administration is discontinued for several days, therapy should be restarted using the initial dosing regimen.

A. *BENIGN PROSTATIC HYPERPLASIA 1-8 mg once daily.* The initial dosage of CARDURA® is 1 mg, given once daily in the a.m. or p.m. Depending on the individual patient's urodynamics and BPH symptomatology, dosage may then be increased to 2 mg and thereafter to 4 mg and 8 mg once daily, the maximum recommended dose for BPH. The recommended titration interval is 1-2 weeks. Blood pressure should be evaluated routinely in these patients.

B. *HYPERTENSION 1-16 mg once daily.* The initial dosage of CARDURA® is 1 mg given once daily. Depending on the individual patient's standing blood pressure response (based on measurements taken at 2-6 hours post-dose and 24 hours post-dose), dosage may then be increased to 2 mg and thereafter if necessary to 4 mg, 8 mg and 16 mg to achieve the desired reduction in blood pressure. **Increases in dose beyond 4 mg increase the likelihood of excessive postural effects including syncope, postural dizziness/vertigo and postural hypotension. At a titrated dose of 16 mg once daily the frequency of postural effects is about 12% compared to 3% for placebo.**

HOW SUPPLIED

CARDURA® (doxazosin mesylate) is available as colored tablets for oral administration. Each tablet contains doxazosin mesylate equivalent to 1 mg (white), 2 mg (yellow), 4 mg (orange) or 8 mg (green) of the active constituent, doxazosin.

CARDURA® TABLETS (doxazosin mesylate) are available as 1 mg (white), 2 mg (yellow), 4 mg (orange) and 8 mg (green) scored tablets.

Bottles of 100: 1 mg (NDC 0049-2750-66)
2 mg (NDC 0049-2760-66)
4 mg (NDC 0049-2770-66)
8 mg (NDC 0049-2780-66)

Unit Dose Packages of 100: 1 mg (NDC 0049-2750-41)
2 mg (NDC 0049-2760-41)
4 mg (NDC 0049-2770-41)
8 mg (NDC 0049-2780-41)

Recommended Storage: Store below 86° F (30° C)

CAUTION: Federal law prohibits dispensing without prescription.

Pfizer

69-4538-00-6

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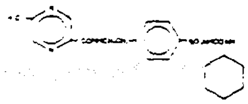
Revised June 1997

GLUCOTROL XL®
(glipizide)
Extended Release Tablets
For Oral Use

DESCRIPTION

Glipizide is an oral blood-glucose-lowering drug of the sulfonylurea class.

The Chemical Abstracts name of glipizide is 1-cyclohexyl-3-[[p-[2-(5-methylpyrazinecarboxamido)ethyl]phenyl]sulfonyl]urea. The molecular formula is $C_{21}H_{27}N_5O_4S$; the molecular weight is 445.55; the structural formula is shown below:



Glipizide is a whitish, odorless powder with a pKa of 5.9. It is insoluble in water and alcohols, but soluble in 0.1 N NaOH; it is freely soluble in dimethylformamide. GLUCOTROL XL® is a registered trademark for glipizide GITS (Glipizide GITS, Gastrointestinal Therapeutic System) is formulated as a once-a-day controlled release tablet for oral use and is designed to deliver 2.5, 5, or 10 mg of glipizide.

Inert ingredients in the 2.5 mg, 5 mg and 10 mg formulations are: polyethylene oxide, hydroxypropyl methylcellulose, magnesium stearate, sodium chloride, red ferric oxide, cellulose acetate, polyethylene glycol, opadry blue (OY-LS-20921) (2.5 mg tablets), opadry white (YS-2-7063) (5 mg and 10 mg tablets) and black ink (S-1-3106).

System Components and Performance

GLUCOTROL XL Extended Release Tablet is similar in appearance to a conventional tablet. It consists, however, of an osmotically active drug core surrounded by a semipermeable membrane. The core itself is divided into two layers: an "active" layer containing the drug, and a "push" layer containing pharmacologically inert (but osmotically active) components. The membrane surrounding the tablet is permeable to water but not to drug or osmotic excipients. As water from the gastrointestinal tract enters the tablet, pressure increases in the osmotic layer and "pushes" against the drug layer, resulting in the release of drug through a small, laser-drilled orifice in the membrane on the drug side of the tablet.

The GLUCOTROL XL Extended Release Tablet is designed to provide a controlled rate of delivery of glipizide into the gastrointestinal lumen which is independent of pH or gastrointestinal motility. The function of the GLUCOTROL XL Extended Release Tablet depends upon the existence of an osmotic gradient between the contents of the bi-layer core and fluid in the GI tract. Drug delivery is essentially constant as long as the osmotic gradient remains constant, and then gradually falls to zero. The biologically inert components of the tablet remain intact during GI transit and are eliminated in the feces as an insoluble shell.

CLINICAL PHARMACOLOGY

Mechanism of Action: Glipizide appears to lower blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets. Extrapancreatic effects also may play a part in the mechanism of action of oral sulfonylurea hypoglycemic drugs. Two extrapancreatic effects shown to be important in the action of glipizide are an increase in insulin sensitivity and a decrease in hepatic glucose production. However, the mechanism by which glipizide lowers blood glucose during long-term administration has not been clearly established. Stimulation of insulin secretion by glipizide in response to a meal is of major importance. The insulinotropic response to a meal is enhanced with GLUCOTROL XL administration in diabetic patients. The postprandial insulin and C-peptide responses continue to be enhanced after at least 6 months of treatment. In 2 randomized, double-blind, dose-response studies comprising a total of 347 patients, there was no significant increase in fasting insulin in all GLUCOTROL XL-treated patients combined compared to placebo, although minor elevations were observed at some doses. There was no increase in fasting insulin over the long term.

Some patients fail to respond initially, or gradually lose their responsiveness to sulfonylurea drugs, including glipizide. Alternatively, glipizide may be effective in some patients who have not responded or have ceased to respond to other sulfonylureas.

Effects on Blood Glucose

The effectiveness of GLUCOTROL XL Extended Release Tablets in type 2 diabetes at doses from 5-60 mg once daily has been evaluated in 4 therapeutic clinical trials each with long-term open extensions involving a total of 598 patients. Once daily administration of 5, 10 and 20 mg produced statistically significant reductions from placebo in hemoglobin A_{1C}, fasting plasma glucose and postprandial glucose in patients with mild to severe type 2 diabetes. In a pooled analysis of the patients treated with 5 mg and 20 mg, the relationship between dose and GLUCOTROL XL's effect of reducing hemoglobin A_{1C} was not established. However, in the case of fasting plasma glucose patients treated with 20 mg had a statistically significant reduction of fasting plasma glucose compared to the 5 mg-treated group.

The reductions in hemoglobin A_{1C} and fasting plasma glucose were similar in younger and older patients. Efficacy of GLUCOTROL XL was not affected by gender, race or weight (as assessed by body mass index). In long term extension trials, efficacy of GLUCOTROL XL was maintained in 81% of patients for up to 12 months.

In an open, two-way crossover study 132 patients were randomly assigned to either GLUCOTROL XL or Glucotrol® for 8 weeks and then crossed over to the other drug for an additional 8 weeks. GLUCOTROL XL administration resulted in significantly lower fasting plasma glucose levels and equivalent hemoglobin A_{1C} levels, as compared to Glucotrol.

Other Effects: It has been shown that GLUCOTROL XL therapy is effective in controlling blood glucose without deleterious changes in the plasma lipoprotein profiles of patients treated for type 2 diabetes.

In a placebo-controlled, crossover study in normal volunteers, glipizide had no antidiuretic activity, and, in fact, led to a slight increase in free water clearance.

Pharmacokinetics and Metabolism: Glipizide is rapidly and completely absorbed following oral administration in an immediate release dosage form. The absolute bioavailability of glipizide was 100% after single oral doses in patients with type 2 diabetes. Beginning 2 to 3 hours after administration of GLUCOTROL XL Extended Release Tablets, plasma drug concentrations gradually rise reaching maximum concentrations within 6 to 12 hours after dosing. With subsequent once daily dosing of GLUCOTROL XL Extended Release Tablets, effective plasma glipizide concentrations are maintained throughout the 24 hour dosing interval with less peak to trough fluctuation than that observed with twice daily dosing of immediate release glipizide. The mean relative bioavailability of glipizide in 21 males with type 2 diabetes after administration of 20 mg GLUCOTROL XL Extended Release Tablets, compared to immediate release Glucotrol (10 mg given twice daily), was 90% at steady-state. Steady-state plasma concentrations were achieved by at least the fifth day of dosing with GLUCOTROL XL Extended Release Tablets in 21 males with type 2 diabetes and patients younger than 65 years. Approximately 1 to 2 days longer were required to reach steady-state in 24 elderly (≥65 years) males and females with type 2 diabetes. No accumulation of drug was observed in patients with type 2 diabetes during chronic dosing with GLUCOTROL XL Extended Release Tablets. Administration of GLUCOTROL XL with food has no effect on the 2 to 3 hour lag time in drug absorption. In a single dose, food effect study in 21 healthy male subjects, the administration of GLUCOTROL XL immediately before a high fat breakfast resulted in a 40% increase in the glipizide mean Cmax value, which was significant, but the effect on the AUC was not significant. There was no change in glucose response between the fed and fasting state. Markedly reduced GI retention times of the GLUCOTROL XL tablets over prolonged periods (e.g., short bowel syndrome) may influence the pharmacokinetic profile of the drug and potentially result in lower plasma concentrations. In a multiple dose study in 26 males with type 2 diabetes, the pharmacokinetics of glipizide were linear over the dose range of 5 to 60 mg of GLUCOTROL XL in that the plasma drug concentrations increased proportionately with dose. In a single dose study in 24 healthy subjects, four 5 mg, two 10 mg, and one 20 mg GLUCOTROL XL Extended Release Tablets were bioequivalent. In a separate single dose study in 36 healthy subjects, four 2.5-mg GLUCOTROL XL Extended Release Tablets were bioequivalent to one 10-mg GLUCOTROL XL Extended Release Tablet.

Glipizide is eliminated primarily by hepatic biotransformation: less than 10% of a dose is excreted as unchanged drug in urine and feces; approximately 90% of a dose is excreted as biotransformation products in urine (80%) and feces (10%). The major metabolites of glipizide are products of aromatic hydroxylation and have no hypoglycemic activity. A minor metabolite which accounts for less than 2% of a dose, an acetylaminoethyl benzene derivative, is reported to have 1/10 to 1/3 as much hypoglycemic activity as the parent compound. The mean total body clearance of glipizide was approximately 3 liters per hour after single intravenous doses in patients with type 2 diabetes. The mean apparent volume of distribution was approximately 10 liters. Glipizide is 98-99% bound to serum proteins, primarily to albumin. The mean terminal elimination half-life of glipizide ranged from 2 to 5 hours after single or multiple doses in patients with type 2 diabetes. There were no significant differences in the pharmacokinetics of glipizide after single dose administration to older diabetic subjects compared to younger healthy subjects. There is only limited information regarding the effects of renal impairment on the disposition of glipizide, and no information regarding the effects of hepatic disease. However, since glipizide is highly protein bound and hepatic biotransformation is the predominant route of elimination, the pharmacokinetics and/or pharmacodynamics of glipizide may be altered in patients with renal or hepatic impairment.

In mice no glipizide or metabolites were detectable autoradiographically in the brain or spinal cord of males or females, nor in the fetuses of pregnant females. In another study, however, very small amounts of radioactivity were detected in the fetuses of rats given labelled drug.

INDICATIONS AND USAGE

GLUCOTROL XL is indicated as an adjunct to diet for the control of hyperglycemia and its associated symptomatology in patients with type 2 diabetes formerly known as non-insulin-dependent diabetes mellitus (NIDDM) or maturity-onset diabetes, after an adequate trial of dietary therapy has proved unsatisfactory. GLUCOTROL XL is indicated when diet alone has been unsuccessful in correcting hyperglycemia, but even after the introduction of the drug in the patient's regimen, dietary measures should continue to be considered as important. In 12 week well-controlled studies there was a maximal average net reduction in hemoglobin A_{1C} of 1.7% in absolute units between placebo-treated and GLUCOTROL XL-treated patients.

In initiating treatment for type 2 diabetes, diet should be emphasized as the primary form of treatment. Caloric restriction and weight loss are essential in the obese diabetic patient. Proper dietary management alone may be effective in controlling blood glucose and symptoms of hyperglycemia. The importance of regular physical activity should also be stressed, cardiovascular risk factors should be identified, and corrective measures taken where possible.

If this treatment program fails to reduce symptoms and/or blood glucose, the use of an oral sulfonylurea should be considered. If additional reduction of symptoms and/or blood glucose is required, the addition of insulin to the treatment regimen should be considered. Use of GLUCOTROL XL must be viewed by both the physician and patient as a treatment in addition to diet, and not as a substitute for diet or as a convenient mechanism for avoiding dietary restraint. Furthermore, loss of blood glucose control on diet alone also may be transient, thus requiring only short-term administration of glipizide.

Some patients fail to respond initially or gradually lose their responsiveness to sulfonylurea drugs, including GLUCOTROL XL. In these cases, the addition of another oral blood glucose-lowering agent to GLUCOTROL XL therapy can be considered. Other approaches that can be considered include substitution of GLUCOTROL XL therapy with that of another oral blood glucose-lowering agent or insulin. GLUCOTROL XL should be discontinued if it no longer contributes to glucose lowering. Judgment of response to therapy should be based on regular clinical and laboratory evaluations.

In considering the use of GLUCOTROL XL in asymptomatic patients, it should be recognized that controlling blood glucose in type 2 diabetes has not been definitely established to be effective in preventing the long-term cardiovascular or neural complications of diabetes. However, in insulin-dependent diabetes mellitus controlling blood glucose has been effective in slowing the progression of diabetic retinopathy, nephropathy, and neuropathy.

CONTRAINDICATIONS

Glipizide is contraindicated in patients with:

1. Known hypersensitivity to the drug.
2. Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.

WARNINGS

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY: The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with type 2 diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups (Diabetes, 19, SUPP. 2: 747-830, 1970).

UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2½ times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of glipizide and of alternative modes of therapy.

Although only one drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

As with any other non-deformable material, caution should be used when administering GLUCOTROL XL Extended Release Tablets in patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of another drug in this non-deformable sustained release formulation.

PRECAUTIONS

General

Renal and Hepatic Disease: The pharmacokinetics and/or pharmacodynamics of glipizide may be affected in patients with impaired renal or hepatic function. If hypoglycemia should occur in such patients, it may be prolonged and appropriate management should be instituted.

GI Disease: Markedly reduced GI retention times of the GLUCOTROL XL Extended Release Tablets may influence the pharmacokinetic profile and hence the clinical efficacy of the drug.

Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes. Renal or hepatic insufficiency may affect the disposition of glipizide and the latter may also diminish gluconeogenic capacity, both of which increase the risk of serious hypoglycemic reactions. Elderly, debilitated or malnourished patients, and those with adrenal or pituitary insufficiency are particularly susceptible to the hypoglycemic action of glucose-lowering drugs. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used. Therapy with a combination of glucose-lowering agents may increase the potential for hypoglycemia.

Loss of Control of Blood Glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of control may occur. At such times, it may be necessary to discontinue glipizide and administer insulin.

The effectiveness of any oral hypoglycemic drug, including glipizide, in lowering blood glucose to a desired level decreases in many patients over a period of time, which may be due to progression of the severity of the diabetes or to diminished responsiveness to the drug. This phenomenon is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective in an individual patient when first given. Adequate adjustment of dose and adherence to diet should be assessed before classifying a patient as a secondary failure.

Laboratory Tests: Blood and urine glucose should be monitored periodically. Measurement of hemoglobin A_{1C} may be useful.

Information for Patients: Patients should be informed that GLUCOTROL XL Extended Release Tablets should be swallowed whole. Patients should not chew, divide or crush tablets. Patients should not be concerned if they occasionally notice in their stool something that looks like a tablet. In the GLUCOTROL XL Extended Release Tablet, the medication is contained within a nonabsorbable shell that has been specially designed to slowly release the drug so the body can absorb it. When this process is completed, the empty tablet is eliminated from the body.

PRECAUTIONS (continued)

Patients should be informed of the potential risks and advantages of GLUCOTROL XL and of alternative modes of therapy. They should also be informed about the importance of adhering to dietary instructions, of a regular exercise program, and of regular testing of urine and/or blood glucose.

The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and responsible family members. Primary and secondary failure also should be explained.

Drug Interactions: The hypoglycemic action of sulfonylureas may be potentiated by certain drugs including nonsteroidal anti-inflammatory agents and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, and beta-adrenergic blocking agents. When such drugs are administered to a patient receiving glipizide, the patient should be observed closely for hypoglycemia. When such drugs are withdrawn from a patient receiving glipizide, the patient should be observed closely for loss of control. In vitro binding studies with human serum proteins indicate that glipizide binds differently than tolbutamide and does not interact with salicylate or dicumarol. However, caution must be exercised in extrapolating these findings to the clinical situation and in the use of glipizide with these drugs.

Certain drugs tend to produce hyperglycemia and may lead to loss of control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving glipizide, the patient should be closely observed for loss of control. When such drugs are withdrawn from a patient receiving glipizide, the patient should be observed closely for hypoglycemia.

A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the intravenous, topical, or vaginal preparations of miconazole is not known. The effect of concomitant administration of Diflucan® (fluconazole) and Glucotrol has been demonstrated in a placebo-controlled crossover study in normal volunteers. All subjects received Glucotrol alone and following treatment with 100 mg of Diflucan® as a single daily oral dose for 7 days. The mean percentage increase in the Glucotrol AUC after fluconazole administration was 56.9% (range: 35 to 81%).

Carcinogenesis, Mutagenesis, Impairment of Fertility: A twenty month study in rats and an eighteen month study in mice at doses up to 75 times the maximum human dose revealed no evidence of drug-related carcinogenicity. Bacterial and in vivo mutagenicity tests were uniformly negative. Studies in rats of both sexes at doses up to 75 times the human dose showed no effects on fertility.

Pregnancy: Pregnancy Category C. Glipizide was found to be mildly fetotoxic in rat reproductive studies at all dose levels (5-50 mg/kg). This fetotoxicity has been similarly noted with other sulfonylureas, such as tolbutamide and tolazamide. The effect is perinatal and believed to be directly related to the pharmacologic (hypoglycemic) action of glipizide. In studies in rats and rabbits no teratogenic effects were found. There are no adequate and well controlled studies in pregnant women. Glipizide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Because recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, many experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nonteratogenic Effects: Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives. If glipizide is used during pregnancy, it should be discontinued at least one month before the expected delivery date.

Nursing Mothers: Although it is not known whether glipizide is excreted in human milk, some sulfonylurea drugs are known to be excreted in human milk. Because the potential for hypoglycemia in nursing infants may exist, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. If the drug is discontinued and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

Pediatric Use: Safety and effectiveness in children have not been established.

Geriatric Use: Of the total number of patients in clinical studies of GLUCOTROL XL, 33 percent were 65 and over. No overall differences in effectiveness or safety were observed between these patients and younger patients, but greater sensitivity of some individuals cannot be ruled out. Approximately 1-2 days longer were required to reach steady-state in the elderly. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.)

ADVERSE REACTIONS

In U.S. controlled studies the frequency of serious adverse experiences reported was very low and causal relationship has not been established.

The 580 patients from 31 to 87 years of age who received GLUCOTROL XL Extended Release Tablets in doses from 5 mg to 60 mg in both controlled and open trials were included in the evaluation of adverse experiences. All adverse experiences reported were tabulated independently of their possible causal relation to medication.

Hypoglycemia: See PRECAUTIONS and OVERDOSAGE sections.

Only 3.4% of patients receiving GLUCOTROL XL Extended Release Tablets had hypoglycemia documented by a blood glucose measurement < 60 mg/dL and/or symptoms believed to be associated with hypoglycemia. In a comparative efficacy study of GLUCOTROL XL and Glucotrol, hypoglycemia occurred rarely with an incidence of less than 1% with both drugs.

In double-blind, placebo-controlled studies the adverse experiences reported with an incidence of 3% or more in GLUCOTROL XL-treated patients include:

Adverse Effect	GLUCOTROL XL (%) (N=278)	Placebo (%) (N=69)
Asthenia	10.1	13.0
Headache	8.6	8.7
Dizziness	6.8	5.8
Nervousness	3.6	2.9
Tremor	3.6	0.0
Diarrhea	5.4	0.0
Flatulence	3.2	1.4

The following adverse experiences occurred with an incidence of less than 3% in GLUCOTROL XL-treated patients:

Body as a whole—pain	Musculoskeletal—arthralgia, leg cramps and myalgia
Nervous system—insomnia, paresthesia, anxiety, depression and hypesthesia	Cardiovascular—syncope
Gastrointestinal—nausea, dyspepsia, constipation and vomiting	Skin—sweating and pruritus
Metabolic—hypoglycemia	Respiratory—rhinitis
	Special senses—blurred vision
	Urogenital—polyuria

Other adverse experiences occurred with an incidence of less than 1% in GLUCOTROL XL-treated patients:

Body as a whole—chills	Cardiovascular—arrhythmia, migraine, flushing and hypertension
Nervous system—hypertonia, confusion, vertigo, somnolence, gait abnormality and decreased libido	Skin—rash and urticaria
Gastrointestinal—anorexia and trace blood in stool	Respiratory—pharyngitis and dyspnea
Metabolic—thirst and edema	Special senses—pain in the eye, conjunctivitis and retinal hemorrhage
	Urogenital—dysuria

Although these adverse experiences occurred in patients treated with GLUCOTROL XL, a causal relationship to the medication has not been established in all cases.

There have been rare reports of gastrointestinal irritation and gastrointestinal bleeding with use of another drug in this non-deformable sustained release formulation, although causal relationship to the drug is uncertain.

The following are adverse experiences reported with immediate release glipizide and other sulfonylureas, but have not been observed with GLUCOTROL XL.

Hematologic: Leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, aplastic anemia, and pancytopenia have been reported with sulfonylureas.

Metabolic: Hepatic porphyria and disulfiram-like reactions have been reported with sulfonylureas. In the mouse, glipizide pretreatment did not cause an accumulation of acetaldehyde after ethanol administration. Clinical experience to date has shown that glipizide has an extremely low incidence of disulfiram-like alcohol reactions.

Endocrine Reactions: Cases of hyponatremia and the syndrome of inappropriate antidiuretic hormone (SIADH) secretion have been reported with glipizide and other sulfonylureas.

ADVERSE REACTIONS (continued)

Laboratory Tests: The pattern of laboratory test abnormalities observed with glipizide was similar to that for other sulfonylureas. Occasional mild to moderate elevations of SGOT, LDH, alkaline phosphatase, BUN and creatinine were noted. One case of jaundice was reported. The relationship of these abnormalities to glipizide is uncertain, and they have rarely been associated with clinical symptoms.

OVERDOSAGE

There is no well-documented experience with GLUCOTROL XL overdosage in humans. There have been no known suicide attempts associated with purposeful overdosing with GLUCOTROL XL. In nonclinical studies the acute oral toxicity of glipizide was extremely low in all species tested (LD_{50} greater than 4 g/kg). Overdosage of sulfonylureas including glipizide can produce hypoglycemia. Mild hypoglycemic symptoms without loss of consciousness or neurologic findings should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring should continue until the physician is assured that the patient is out of danger. Severe hypoglycemic reactions with coma, seizure, or other neurological impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalization. If hypoglycemic coma is diagnosed or suspected, the patient should be given rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of a more dilute (10%) glucose solution at a rate that will maintain the blood glucose at a level above 100 mg/dL. Patients should be closely monitored for a minimum of 24 to 48 hours since hypoglycemia may recur after apparent clinical recovery. Clearance of glipizide from plasma may be prolonged in persons with liver disease. Because of the extensive protein binding of glipizide, dialysis is unlikely to be of benefit.

DOSAGE AND ADMINISTRATION

There is no fixed dosage regimen for the management of diabetes mellitus with GLUCOTROL XL Extended Release Tablet or any other hypoglycemic agent. Glycemic control should be monitored with hemoglobin A_{1c} and/or blood glucose levels to determine the minimum effective dose for the patient; to detect primary failure, i.e., inadequate lowering of blood glucose at the maximum recommended dose of medication; and to detect secondary failure, i.e., loss of an adequate blood-glucose-lowering response after an initial period of effectiveness. Home blood glucose monitoring may also provide useful information to the patient and physician. Short-term administration of GLUCOTROL XL Extended Release Tablet may be sufficient during periods of transient loss of control in patients usually controlled on diet.

In general, GLUCOTROL XL should be given with breakfast.

Recommended Dosing: The recommended starting dose of GLUCOTROL XL is 5 mg per day, given with breakfast. The recommended dose for geriatric patients is also 5 mg per day.

Dosage adjustment should be based on laboratory measures of glycemic control. While fasting blood glucose levels generally reach steady-state following initiation or change in GLUCOTROL XL dosage, a single fasting glucose determination may not accurately reflect the response to therapy. In most cases, hemoglobin A_{1c} level measured at three month intervals is the preferred means of monitoring response to therapy.

Hemoglobin A_{1c} should be measured as GLUCOTROL XL therapy is initiated at the 5 mg dose and repeated approximately three months later. If the result of this test suggests that glycemic control over the preceding three months was inadequate, the GLUCOTROL XL dose may be increased. Subsequent dosage adjustments should be made on the basis of hemoglobin A_{1c} levels measured at three month intervals. If no improvement is seen after three months of therapy with a higher dose, the previous dose should be resumed. Decisions which utilize fasting blood glucose to adjust GLUCOTROL XL therapy should be based on at least two or more similar consecutive values obtained seven days or more after the previous dose adjustment.

Most patients will be controlled with 5 mg to 10 mg taken once daily. However, some patients may require up to the maximum recommended daily dose of 20 mg. While the glycemic control of selected patients may improve with doses which exceed 10 mg, clinical studies conducted to date have not demonstrated an additional group average reduction of hemoglobin A_{1c} beyond what was achieved with the 10 mg dose.

Based on the results of a randomized crossover study, patients receiving immediate release glipizide may be switched safely to GLUCOTROL XL Extended Release Tablets once-a-day at the nearest equivalent total daily dose. Patients receiving immediate release Glucotrol also may be titrated to the appropriate dose of GLUCOTROL XL starting with 5 mg once daily. The decision to switch to the nearest equivalent dose or to titrate should be based on clinical judgment.

In elderly patients, debilitated or malnourished patients, and patients with impaired renal or hepatic function, the initial and maintenance dosing should be conservative to avoid hypoglycemic reactions (see PRECAUTIONS section).

When GLUCOTROL XL is used in combination with other oral blood glucose-lowering agents, the second agent should be added at the lowest recommended dose and patients should be observed carefully. Titration of the added oral agent should be based on clinical judgment.

Patients Receiving Insulin: As with other sulfonylurea-class hypoglycemics, many patients with stable type 2 diabetes receiving insulin may be transferred safely to treatment with GLUCOTROL XL Extended Release Tablets. When transferring patients from insulin to GLUCOTROL XL, the following general guidelines should be considered.

For patients whose daily insulin requirement is 20 units or less, insulin may be discontinued and GLUCOTROL XL therapy may begin at usual dosages. Several days should elapse between titration steps.

For patients whose daily insulin requirement is greater than 20 units, the insulin dose should be reduced by 50% and GLUCOTROL XL therapy may begin at usual dosages. Subsequent reductions in insulin dosage should depend on individual patient response. Several days should elapse between titration steps.

During the insulin withdrawal period, the patient should test urine samples for sugar and ketone bodies at least three times daily. Patients should be instructed to contact the prescriber immediately if these tests are abnormal. In some cases, especially when the patient has been receiving greater than 40 units of insulin daily, it may be advisable to consider hospitalization during the transition period.

Patients Receiving Other Oral Hypoglycemic Agents: As with other sulfonylurea-class hypoglycemics, no transition period is necessary when transferring patients to GLUCOTROL XL Extended Release Tablets. Patients should be observed carefully (1-2 weeks) for hypoglycemia when being transferred from longer half-life sulfonylureas (e.g., chlorpropamide) to GLUCOTROL XL due to potential overlapping of drug effect.

HOW SUPPLIED

GLUCOTROL XL® (glipizide) Extended Release Tablets are supplied as 2.5 mg, 5 mg, and 10 mg round, biconvex tablets and imprinted with black ink as follows:

- 2.5 mg tablets are blue and imprinted with "GLUCOTROL XL 2.5" on one side.
  - Bottles of 30: NDC 0049-1620-30
- 5 mg tablets are white and imprinted with "GLUCOTROL XL 5" on one side.
  - Bottles of 100: NDC 0049-1550-66
  - Bottles of 500: NDC 0049-1550-73
- 10 mg tablets are white and imprinted with "GLUCOTROL XL 10" on one side.
  - Bottles of 100: NDC 0049-1560-66
  - Bottles of 500: NDC 0049-1560-73

Recommended Storage: The tablets should be protected from moisture and humidity and stored at controlled room temperature, 59° to 86°F (15° to 30°C).

R_x only

Pfizer

65-4951-00-5

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Revised August 1999

CARDURA®
(doxazosin mesylate) Scored Tablets 1 mg, 2 mg, 4 mg, 8 mg

- Proven control of hypertension—when used alone or in combination[4-6]
- Comparable efficacy with other major antihypertensive agents[5]
- Does not compromise the lipid profile[8]
- Does not compromise blood sugar or insulin levels[9]
- Controls blood pressure in hypertensive patients with diabetes[7]
- Least expensive alpha blocker—about $1.00 per day[13*]

WHEN DIET ALONE FAILS IN TYPE 2 DIABETES...

ONCE DAILY **GLUCOTROL XL**
(glipizide) extended release tablets

- Effective blood glucose control—with lower fasting insulin levels than glyburide[10,11]
- No weight gain[10,14]
- No adverse effects on the lipid profile[10,12]
- Least expensive branded oral hypoglycemic agent[15*]

As with all sulfonylureas, hypoglycemia may occur.

*Cost comparison does not imply comparable efficacy. Actual cost to patient may vary.

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Please see full prescribing information for CARDURA and Glucotrol XL on last pages.

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Printed in USA/September 1999

Pfizer U.S. Pharmaceuticals

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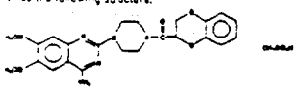
Cardura®

(doxazosin mesylate)
Tablets

DESCRIPTION

CARDURA® (doxazosin mesylate) is a quinazoline compound that is a selective inhibitor of the alpha$_1$ subtype of alpha adrenergic receptors. The chemical name of doxazosin mesylate is 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(1,4-benzodioxan-2-ylcarbonyl) piperazine methanesulfonate. The empirical formula for doxazosin mesylate is $C_{23}H_{25}N_5O_5 \cdot CH_4O_3S$ and the molecular weight is 547.6. It has the following structure:



CARDURA® (doxazosin mesylate) is freely soluble in dimethylsulfoxide, soluble in dimethylformamide, slightly soluble in methanol, ethanol, and water (0.8% at 25°C), and very slightly soluble in acetone and methylene chloride. CARDURA® is available as colored tablets for oral use and contains 1 mg (white), 2 mg (yellow), 4 mg (orange) and 8 mg (green) of doxazosin as the free base.

The inactive ingredients for all tablets are: microcrystalline cellulose, lactose, sodium starch glycolate, magnesium stearate and sodium lauryl sulfate. The 2 mg tablet contains D & C yellow 10 and FD & C yellow 6, the 4 mg tablet contains FD & C yellow 6, the 8 mg tablet contains FD & C blue 1 and D & C yellow 10.

CLINICAL PHARMACOLOGY

Pharmacodynamics

A. Benign Prostatic Hyperplasia (BPH)

Benign prostatic hyperplasia (BPH) is a common cause of urinary outflow obstruction in aging males. Severe BPH may lead to urinary retention and renal damage. A static and a dynamic component contribute to the symptoms and reduced urinary flow rate associated with BPH. The static component is related to an increase in prostate size caused, in part, by a proliferation of smooth muscle cells in the prostatic stroma. However, the severity of BPH symptoms and the degree of urethral obstruction do not correlate well with the size of the prostate. The dynamic component of BPH is associated with an increase in smooth muscle tone in the prostate and bladder neck. The degree of tone in this area is mediated by the alpha$_1$ adrenoceptor, which is present in high density in the prostatic stroma, prostatic capsule and bladder neck. Blockade of the alpha$_1$ receptor decreases urethral resistance and may relieve the obstruction and BPH symptoms. In the human prostate, CARDURA® antagonizes phenylephrine (alpha$_1$ agonist)-induced contractions, *in vitro*, and binds with high affinity to the alpha$_{1a}$ adrenoceptor. The receptor subtype is thought to be the predominant functional type in the prostate. CARDURA® acts within 1-2 weeks to decrease the severity of BPH symptoms and improve urinary flow rate. Since alpha$_1$ adrenoceptors are of low density in the urinary bladder (apart from the bladder neck), CARDURA® should maintain bladder contractility.

The efficacy of CARDURA® was evaluated extensively in over 900 patients with BPH in double-blind, placebo-controlled trials. CARDURA® treatment was superior to placebo in improving patient symptoms and urinary flow rate. Significant relief with CARDURA® was seen as early as one week into the treatment regimen, with CARDURA® treated patients (N=173) showing a significant ($p<0.01$) increase in maximum flow rate of 0.8 mL/sec compared to a decrease of 0.5 mL/sec in the placebo group (N=41). In long-term studies improvement was maintained for up to 2 years of treatment. In 66-71% of patients, improvements above baseline were seen in both symptoms and maximum urinary flow rate.

In three placebo-controlled studies of 14-16 weeks duration obstructive symptoms (hesitation, intermittency, dribbling, weak urinary stream, incomplete emptying of the bladder) and irritative symptoms (nocturia, daytime frequency, urgency, burning) of BPH were evaluated at each visit by patient-assessed symptom questionnaires. The bothersomeness of symptoms was measured with a modified Boyarsky questionnaire. Symptom severity/frequency was assessed using a modified Boyarsky questionnaire or an AUA-based questionnaire. Uroflowmetric evaluations were performed at times of peak (2-6 hours post-dose) and/or trough (24 hours post-dose) plasma concentrations of CARDURA®.

The results from the three placebo-controlled studies (N=609) showing significant efficacy with 4 mg and 8 mg doxazosin are summarized in Table 1. In all three studies, CARDURA® resulted in statistically significant relief of obstructive and irritative symptoms compared to placebo. Statistically significant improvements of 2.3-3.3 mL/sec in maximum flow rate were seen with CARDURA® in Studies 1 and 2, compared to 0.1-0.7 mL/sec with placebo.

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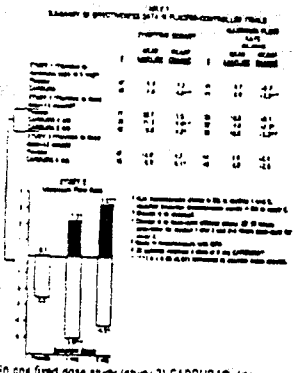
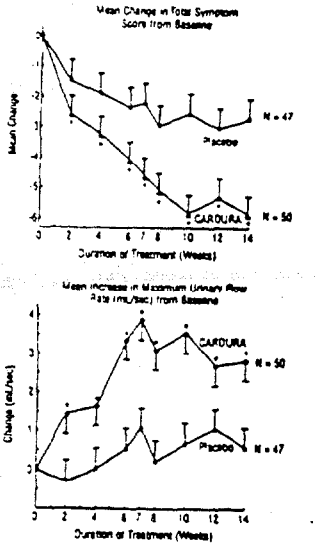


In one fixed dose study (study 2) CARDURA® (doxazosin mesylate) therapy (4-8 mg, once daily) resulted in a significant and sustained improvement in maximum urinary flow rate of 2.3-3.3 mL/sec (Table 1) compared to placebo (0.1 mL/sec). In this study, the only study in which weekly evaluations were made, significant improvement with CARDURA® vs. placebo was seen after one week. The proportion of patients who responded with a maximum flow rate improvement of ≥ 3 mL/sec was significantly larger with CARDURA® (34-42%) than placebo (13-17%). A significantly greater improvement was also seen in average flow rate with CARDURA® (1.5 mL/sec) than with placebo (0.2 mL/sec). The onset and time course of symptom relief and increased urinary flow from study 1 are illustrated in Figure 1.

Figure 1—Study 1



* $p < 0.05$ Compared to Placebo; + $p < 0.05$ Compared to Baseline; Doxazosin Titration to Maximum of 8 mg.

In BPH patients (N=450) treated for up to 2 years in open-label studies, CARDURA® therapy resulted in significant improvement above baseline in urinary flow rates and BPH symptoms. The significant effects of CARDURA® were maintained over the entire treatment period.

Although blockade of alpha$_1$ adrenoceptors also lowers blood pressure in hypertensive patients with increased peripheral vascular resistance, CARDURA® treatment of normotensive men with BPH did not result in a clinically significant blood pressure lowering effect (Table 2). The proportion of normotensive patients with a sitting systolic blood pressure less than 90 mmHg and/or diastolic blood pressure less than 60 mmHg at any time during treatment with CARDURA® 1-8 mg once daily was 6.7% with doxazosin and not significantly different (statistically) from that with placebo (5%).

TABLE 2

Mean Changes in Blood Pressure from Baseline to the Mean of the Final Efficacy Phase in Normotensive (Diastolic BP <90 mmHg) in Two Double-blind, Placebo-controlled U.S. Studies with CARDURA® 1-8 mg once daily.

	PLACEBO (N=83)		CARDURA® (N=163)	
Supine BP (mmHg)	Baseline	Change	Baseline	Change
Systolic	128.4	-1.4	128.8	-4.8*
Diastolic	79.2	-1.2	79.6	-2.4*
Standing BP (mmHg)	Baseline	Change	Baseline	Change
Systolic	128.5	-0.6	128.5	-3.3*
Diastolic	80.5	-0.7	80.4	-2.8*

* $p \leq 0.05$ compared to placebo

B. Hypertension

The mechanism of action of CARDURA® (doxazosin mesylate) is selective blockade of the alpha$_1$ (postjunctional) subtype of adrenergic receptors. Studies in normal human subjects have shown that doxazosin competitively antagonized the pressor effects of phenylephrine (an alpha$_1$ agonist) and the systolic pressor effect of norepinephrine. Doxazosin and prazosin have similar abilities to antagonize phenylephrine. The antihypertensive effect of CARDURA® results from a decrease in systemic vascular resistance. The parent compound doxazosin is primarily responsible for the antihypertensive activity. The low plasma concentrations of known active and inactive metabolites of doxa-

Systolic	28.4	-1.4	-3.5	+0.2
Diastolic	19.2	-1.2	-1.5	-2.4*
Standing (2 hours)	Baseline	Change	Baseline	Change
Systolic	18.5	-1.5	18.5	-3.3*
Diastolic	10.5	-0.7	90.4	-2.6*

*p ≤ 0.05 compared to placebo

B. Hypertension

The mechanism of action of CARDURA® (doxazosin mesylate) is selective blockade of the alpha$_1$ postsynaptic subtype of adrenergic receptors. Studies in normal human subjects have shown that doxazosin competitively antagonized the pressor effects of phenylephrine (an alpha$_1$ agonist) and the systolic pressor effect of norepinephrine. Doxazosin and prazosin have similar abilities to antagonize phenylephrine. The antihypertensive effect of CARDURA® results from a decrease in systemic vascular resistance. The parent compound doxazosin is primarily responsible for the antihypertensive activity. The low plasma concentrations of known active and inactive metabolites of doxazosin (2-piperazinyl, 6'- and 7'-hydroxy and 5- and 7-O-desmethyl compounds) compared to parent drug indicate that the contribution of even the most potent compound (6'-hydroxy) to the antihypertensive effect of doxazosin in man is probably small. The 6'- and 7'-hydroxy metabolites have demonstrated antioxidant properties at concentrations of 5 µM in vitro.

Administration of CARDURA® results in a reduction in systemic vascular resistance. In patients with hypertension there is little change in cardiac output. Maximum reductions in blood pressure usually occur 2-6 hours after dosing and are associated with a small increase in standing heart rate. Like other alpha$_1$-adrenergic blocking agents, doxazosin has a greater effect on blood pressure and heart rate in the standing position.

In a pooled analysis of placebo-controlled hypertension studies with about 300 hypertensive patients per treatment group, doxazosin, at doses of 1-16 mg given once daily, lowered blood pressure at 24 hours by about 10/8 mmHg compared to placebo in the standing position and about 9/5 mmHg in the supine position. Peak blood pressure effects (1-6 hours) were larger by about 50-75% (i.e., trough values were about 55-70% of peak effect), with the larger peak-trough differences seen in systolic pressures. There was no apparent difference in the blood pressure response of Caucasians and blacks or of patients above and below age 65. In these predominantly normochoresterolemic patients doxazosin produced small reductions in total serum cholesterol (2-3%), LDL cholesterol (4%), and a similarly small increase in HDL/total cholesterol ratio (4%). The clinical significance of these findings is uncertain. In the same patient population, patients receiving CARDURA® gained a mean of 0.6 kg compared to a mean loss of 0.1 kg for placebo patients.

Pharmacokinetics

After oral administration of therapeutic doses, peak plasma levels of CARDURA® (doxazosin mesylate) occur at about 2-3 hours. Bioavailability is approximately 65%, reflecting first pass metabolism of doxazosin by the liver. The effect of food on the pharmacokinetics of CARDURA® was examined in a crossover study with twelve hypertensive subjects. Reductions of 18% in mean maximum plasma concentration and 12% in the area under the concentration-time curve occurred when CARDURA® was administered with food. Neither of these differences was statistically or clinically significant.

CARDURA® is extensively metabolized in the liver, mainly by O-demethylation of the quinazoline nucleus or hydroxylation of the benzodioxan moiety. Although several active metabolites of doxazosin have been identified, the pharmacokinetics of these metabolites have not been characterized. In a study of two subjects administered radiolabeled doxazosin 2 mg orally and 1 mg intravenously on two separate occasions, approximately 63% of the dose was eliminated in the feces and 9% of the dose was found in the urine. On average only 4.8% of the dose was excreted as unchanged drug in the feces and only a trace of the total radioactivity in the urine was attributed to unchanged drug. At the plasma concentrations achieved by therapeutic doses, approximately 98% of the circulating drug is bound to plasma proteins.

Plasma elimination of doxazosin is biphasic, with a terminal elimination half-life of about 22 hours. Steady-state studies in hypertensive patients given doxazosin doses of 2-16 mg once daily showed linear kinetics and dose proportionality. In two studies, following the administration of 2 mg orally once daily, the mean accumulation ratios (steady-state AUC vs. first dose AUC) were 1.2 and 1.7. Enterohepatic recycling is suggested by secondary peaking of plasma doxazosin concentrations.

In a crossover study in 24 normotensive subjects, the pharmacokinetics and safety of doxazosin were shown to be similar with morning and evening dosing regimens. The area under the curve after morning dosing was, however, 11% less than that after evening dosing and the time to peak concentration after evening dosing occurred significantly later than that after morning dosing (5.8 hr vs. 3.5 hr).

The pharmacokinetics of CARDURA® (doxazosin mesylate) in young (<65 years) and elderly (≥65 years) subjects were similar for plasma half-life values and oral clearance. Pharmacokinetic studies in elderly patients and patients with renal impairment have shown no significant alterations compared to younger patients with normal renal function. Administration of a single 2 mg dose to patients with cirrhosis (Child-Pugh Class A) showed a 40% increase in exposure to doxazosin. There are only limited data on the effects of drugs known to influence the hepatic metabolism of doxazosin (e.g., cimetidine (see PRECAUTIONS)). As with any drug wholly metabolized by the liver, use of CARDURA® in patients with altered liver function should be undertaken with caution.

In two placebo-controlled studies, of normotensive and hypertensive BPH patients, in which doxazosin was administered in the morning and the titration interval was two weeks and one week, respectively, trough plasma concentrations of CARDURA® were similar in the two populations. Linear kinetics and dose proportionality were observed.

INDICATIONS AND USAGE

A. *Benign Prostatic Hyperplasia (BPH).* CARDURA® is indicated for the treatment of both the urinary outflow obstruction and obstructive and irritative symptoms associated with BPH: obstructive symptoms (hesitation, intermittency, dribbling, weak urinary stream, incomplete emptying of the bladder) and irritative symptoms (nocturia, daytime frequency, urgency, burning). CARDURA® may be used in all BPH patients whether hypertensive or normotensive. In patients with hypertension and BPH, both conditions were effectively treated with CARDURA® monotherapy. CARDURA® provides rapid improvement in symptoms and urinary flow rate in 66-71% of patients. Sustained improvements with CARDURA® were seen in patients treated for up to 14 weeks in double-blind studies and up to 2 years in open-label studies.

B. *Hypertension.* CARDURA® (doxazosin mesylate) is also indicated for the treatment of hypertension. CARDURA® may be used alone or in combination with diuretics, beta-

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CONTRAINDICATIONS

CARDURA® is contraindicated in patients with a previous hypersensitivity to quinazolines (e.g., prazosin, terazosin).

WARNINGS

Syncope and "First-dose" Effect: Doxazosin, like other alpha-adrenergic blocking agents, can cause marked hypotension, especially in the upright position, with syncope and other postural symptoms such as dizziness. Marked orthostatic effects are most common with the first dose but can also occur when there is a dosage increase, or if therapy is interrupted for more than a few days. To decrease the likelihood of excessive hypotension and syncope, it is essential that treatment be initiated with the 1 mg dose. The 2, 4, and 8 mg tablets are not for initial therapy. Dosage should then be adjusted slowly (see DOSAGE AND ADMINISTRATION section) with evaluations and increases in dose every two weeks to the recommended dose. Additional antihypertensive agents should be added with caution.

Patients being titrated with doxazosin should be cautioned to avoid situations where injury could result should syncope occur, during both the day and night.

In an early investigational study of the safety and tolerance of increasing daily doses of doxazosin in normotensives beginning at 1 mg/day, only 2 of 8 subjects could tolerate more than 2 mg/day without experiencing symptomatic postural hypotension. In another study of 24 healthy normotensive male subjects receiving initial doses of 2 mg/day of doxazosin, seven (29%) of the subjects experienced symptomatic postural hypotension between 0.5 and 6 hours after the first dose necessitating termination of the study. In this study, 2 of the normotensive subjects experienced syncope. Subsequent trials in hypertensive patients always began doxazosin dosing at 1 mg/day resulting in a 4% incidence of postural side effects at 1 mg/day with no cases of syncope.

In multiple dose clinical trials in hypertension involving over 1500 hypertensive patients with dose titration every one to two weeks, syncope was reported in 0.7% of patients. None of these events occurred at the starting dose of 1 mg and 1.2% (8/564) occurred at 16 mg/day.

In placebo-controlled clinical trials in BPH, 3 out of 665 patients (0.5%) taking doxazosin reported syncope. Two of the patients were taking 1 mg doxazosin, while one patient was taking 2 mg doxazosin when syncope occurred. In the open-label long-term extension follow-up of approximately 450 BPH patients, there were 3 reports of syncope (0.7%). One patient was taking 2 mg, one patient was taking 8 mg and one patient was taking 12 mg when syncope occurred. In a clinical pharmacology study, one subject receiving 2 mg experienced syncope.

If syncope occurs, the patient should be placed in a recumbent position and treated supportively as necessary.

Priapism: Rarely (frequency less frequently than once in every several thousand patients), alpha$_1$-antagonists such as doxazosin have been associated with priapism (painful penile erection sustained for hours and unrelieved by sexual intercourse or masturbation). Because this condition can lead to permanent impotence if not promptly treated, patients must be advised about the seriousness of the condition (see PRECAUTIONS: Information for Patients).

PRECAUTIONS

General:

Prostate Cancer: Carcinoma of the prostate causes many of the symptoms associated with BPH and the two disorders frequently co-exist. Carcinoma of the prostate should therefore be ruled out prior to commencing therapy with CARDURA®.

Orthostatic Hypotension: While syncope is the most severe orthostatic effect of CARDURA®, other symptoms of lowered blood pressure, such as dizziness, lightheadedness, or vertigo can occur, especially at initiation of therapy or at the time of dose increases.

a) Hypertension

These symptoms were common in clinical trials in hypertension, occurring in up to 23% of all patients treated and causing discontinuation of therapy in about 2%.

In placebo-controlled titration trials in hypertension, orthostatic effects were minimized by beginning therapy at 1 mg per day and titrating every two weeks to 2, 4, or 8 mg per day. There was an increased frequency of orthostatic effects in patients given 8 mg or more, 10%, compared to 5% at 1-4 mg and 3% in the placebo group.

b) Benign Prostatic Hyperplasia

In placebo-controlled trials in BPH, the incidence of orthostatic hypotension with doxazosin was 0.3% and did not increase with increasing dosage (to 8 mg/day). The incidence of discontinuations due to hypotensive or orthostatic symptoms was 3.3% with doxazosin and 1% with placebo. The titration interval in these studies was one to two weeks.

Patients in occupations in which orthostatic hypotension could be dangerous should be treated with particular caution. As alone, antagonists can cause orthostatic effects, it is important to evaluate standing blood pressure two minutes after standing and patients should be advised to exercise care when arising from a supine or sitting position.

If hypotension occurs, the patient should be placed in the supine position and, if this measure is inadequate, volume expansion with intravenous fluids or vasopressor therapy may be used. A transient hypotensive response is not a contraindication to further doses of CARDURA® (doxazosin mesylate).

Information for Patients (See Patient Package Insert):

Patients should be made aware of the possibility of syncope and orthostatic symptoms, especially at the initiation of

therapy and urged to avoid driving or hazardous tasks for 24 hours after the first dose after a dosage increase, and after interruption of therapy when treatment is resumed. They should be cautioned to avoid situations where injury could result should syncope occur during initiation of doxazosin therapy. They should also be advised of the need to sit or lie down when symptoms of lowered blood pressure occur, although these symptoms are not always orthostatic and to be careful when rising from a sitting or lying position. If dizziness, lightheadedness, or palpitations are bothersome they should be reported to the physician, so that dose adjustment can be considered. Patients should also be told that drowsiness or somnolence can occur with CARDURA® (doxazosin mesylate) or any selective alpha$_1$ adrenoceptor antagonist, requiring caution in people who must drive or operate heavy machinery.

Patients should be advised about the ... bility of priapism as a result of treatment with alpha$_1$ antagonists. Patients should know that this adverse event is very rare. If they experience priapism, it should be brought to immediate medical attention for, if not treated promptly, it can lead to permanent erectile dysfunction (impotence).

Drug/Laboratory Test Interactions: CARDURA® does not affect the plasma concentration of prostate specific antigen in patients treated for up to 3 years. Both doxazosin, an alpha$_1$ inhibitor, and finasteride, a 5-alpha reductase inhibitor are highly protein bound and hepatically metabolized. There is no definitive controlled clinical experience on the concomitant use of alpha$_1$ inhibitors and 5-alpha reductase inhibitors at this time.

Impaired Liver Function: CARDURA® should be administered with caution to patients with evidence of impaired hepatic function or to patients receiving drugs known to influence hepatic metabolism (see CLINICAL PHARMACOLOGY).

Leukopenia/Neutropenia: Analysis of hematologic data from hypertensive patients receiving CARDURA® in controlled hypertension clinical trials showed that the mean WBC (N=4741) and mean neutrophil counts (N=4419) were decreased by 2.4% and 1.0%, respectively, compared to placebo, a phenomenon seen with other alpha blocking drugs. In BPH patients the incidence of clinically significant WBC abnormalities was 0.4% (2/459) with CARDURA® and 0% (0/147) with placebo, with no statistically significant difference between the two treatment groups. A search through a data base of 2400 hypertensive patients and 565 BPH patients revealed 4 hypertensives in which drug-related neutropenia could not be ruled out and one BPH patient in which drug related leukopenia could not be ruled out. Two hypertensives had a single low value on the last day of treatment. Two hypertensives had stable, non-progressive neutrophil counts in the 1000/mm^3 range over periods of 20 and 40 weeks. One BPH patient had a decrease from a WBC count of 4800/mm^3 to 2700/mm^3 at the end of the study; there was no evidence of clinical impairment. In cases where follow-up was available the WBCs and neutrophil counts returned to normal after discontinuation of CARDURA® No patients became symptomatic as a result of the low WBC or neutrophil counts.

Drug Interactions: Most (98%) of plasma doxazosin is protein bound. In vitro data in human plasma indicate that CARDURA® has no effect on protein binding of digoxin, warfarin, phenytoin or indomethacin. There is no information on the effect of other highly plasma protein bound drugs on doxazosin binding. CARDURA® has been administered without any evidence of an adverse drug interaction to patients receiving thiazide diuretics, beta-blocking agents, and nonsteroidal anti-inflammatory drugs. In a placebo-controlled trial in normal volunteers, the administration of a single 1 mg dose of doxazosin on day 1 of a four-day regimen of oral cimetidine (400 mg twice daily) resulted in a 10% increase in mean AUC of doxazosin ($p=0.005$), and a slight but not statistically significant increase in mean C_{max} and mean half-life of doxazosin. The clinical significance of this increase in doxazosin AUC is unknown.

In clinical trials, CARDURA® tablets have been administered to patients on a variety of concomitant medications; while no formal interaction studies have been conducted, no interactions were observed. CARDURA® tablets have been used with the following drugs or drug classes: 1) analgesic/anti-inflammatory (e.g., acetaminophen, aspirin, codeine and codeine combinations, ibuprofen, indomethacin); 2) antibiotics (e.g., erythromycin, trimethoprim and sulfamethoxazole, amoxicillin); 3) antihistamines (e.g., chlorpheniramine); 4) cardiovascular agents (e.g., atenolol, hydrochlorothiazide, propranolol); 5) corticosteroids; 6) gastrointestinal agents (e.g., antacids); 7) hypoglycemics and endocrine drugs; 8) sedatives and tranquilizers (e.g., diazepam); 9) cold and flu remedies.

Cardiac Toxicity in Animals: An increased incidence of myocardial necrosis or fibrosis was observed by Sprague-Dawley rats after 6 months of dietary administration at concentrations calculated to provide 80 mg doxazosin/kg/day and after 12 months of dietary administration at concentrations calculated to provide 40 mg doxazosin/kg/day (AUC exposure in rats 8 times the human AUC exposure with a 12 mg/day therapeutic dose). Myocardial fibrosis was observed in both rats and mice treated in the same manner with 40 mg doxazosin/kg/day for 18 months (exposure 8 times human AUC exposure in rats and somewhat equivalent to human C_{max} exposure in mice). No cardiotoxicity was observed at lower doses (up to 10 or 20 mg/kg/day, depending on the study) in either species. These lesions were not observed after 12 months of oral dosing in dogs at maximum doses of 20 mg/kg/day (maximum plasma concentrations (C_{max}) in dogs 14 times the C_{max} exposure in humans receiving a 12 mg/day therapeutic dose) and in Wistar rats at doses of 100 mg/kg/day (C_{max} exposures 15 times human C_{max} exposure with a 12 mg/day therapeutic dose). There is no evidence that similar lesions occur in humans.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Chronic dietary administration (up to 24 months) of doxazosin mesylate at maximally tolerated doses of 40 mg/kg/day in rats and 120 mg/kg/day in mice revealed no evidence of carcinogenic potential. The highest doses evaluated in the rat and mouse studies are associated with AUCs (a measure of systemic exposure) that are 8 times and 4 times, respectively, the human AUC at a dose of 16 mg/day.

Mutagenicity studies revealed no drug- or metabolite-related effects at either chromosomal or subchromosomal levels.

Studies in rats showed reduced fertility in males treated with doxazosin at oral doses of 20 (but not 5 or 10) mg/kg/day, about 4 times the AUC exposures obtained with a 12 mg/day human dose. This effect was reversible within

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Studies in rats showed reduced fertility in males treated with doxazosin at oral doses of 20 (but not 5 or 10) mg/kg/day, about 4 times the AUC exposures obtained with a 12 mg/day human dose. This effect was reversible within two weeks of drug withdrawal. There have been no reports of any effects of doxazosin on male fertility in humans.

Pregnancy: Teratogenic Effects. Pregnancy Category C. Studies in pregnant rabbits and rats at daily oral doses of up to 41 and 20 mg/kg, respectively (plasma drug concentrations 10 and 4 times human C_{max} and AUC exposures with a 12 mg/day therapeutic dose), have revealed no evidence of harm to the fetus. A dosage regimen of 82 mg/kg/day in the rabbit was associated with reduced fetal survival. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, CARDURA® should be used during pregnancy only if clearly needed.

Radioactivity was found to cross the placenta following oral administration of labeled doxazosin to pregnant rats.

Nonteratogenic Effects. In peri-postnatal studies in rats, postnatal development at maternal doses of 40 or 50 mg/kg/day of doxazosin (8 times human AUC exposure with a 12 mg/day therapeutic dose) was delayed as evidenced by slower body weight gain and a slightly later appearance of anatomical features and reflexes.

Nursing Mothers: Studies in lactating rats given a single oral dose of 1 mg/kg of [2-^{14}C]-CARDURA® indicate that doxazosin accumulates in rat breast milk with a maximum concentration about 20 times greater than the maternal plasma concentration. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when CARDURA® is administered to a nursing mother.

Pediatric Use: The safety and effectiveness of CARDURA® as an antihypertensive agent have not been established in children.

Use in Elderly: The safety and effectiveness profile of CARDURA® in BPH was similar in the elderly (age ≥ 65 years) and younger (age < 65 years) patients.

ADVERSE REACTIONS

A. Benign Prostatic Hyperplasia

The incidence of adverse events has been ascertained from worldwide clinical trials in 965 BPH patients. The incidence rates presented below (Table 3) are based on combined data from seven placebo-controlled trials involving once daily administration of CARDURA® (doxazosin mesylate) in doses of 1-16 mg in hypertensives and 0.5-8 mg in normotensives. The adverse events when the incidence in the CARDURA® group was at least 1% are summarized in Table 3. No significant difference in the incidence of adverse events compared to placebo was seen except for dizziness, fatigue, hypotension, edema and dysuresis. Dizziness and dysuresis appeared to be dose-related.

TABLE 3
ADVERSE REACTIONS DURING
PLACEBO-CONTROLLED STUDIES
BENIGN PROSTATIC HYPERPLASIA

Body System	CARDURA® (N=665)	PLACEBO (N=300)
BODY AS A WHOLE		
Back pain	1.8%	2.0%
Chest pain	1.2%	0.7%
Fatigue	8.0%*	1.7%
Headache	9.9%	9.0%
Influenza-like symptoms	1.1%	1.0%
Pain	2.0%	1.0%
CARDIOVASCULAR SYSTEM		
Hypotension	1.7%*	0.0%
Palpitation	1.2%	0.3%
DIGESTIVE SYSTEM		
Abdominal Pain	2.4%	2.0%
Diarrhea	2.3%	2.0%
Dyspepsia	1.7%	1.7%
Nausea	1.5%	0.7%
METABOLIC AND NUTRITIONAL DISORDERS		
Edema	2.7%*	0.7%
NERVOUS SYSTEM		
Dizziness†	15.6%*	9.0%
Mouth Dry	1.4%	0.3%
Somnolence	3.0%	1.0%
RESPIRATORY SYSTEM		
Dyspnea	2.6%*	0.3%
Respiratory Disorder	1.1%	0.7%
SPECIAL SENSES		
Vision Abnormal	1.4%	0.7%
UROGENITAL SYSTEM		
Impotence	1.1%	1.0%
Urinary Tract Infection	1.4%	2.3%
SKIN & APPENDAGES		
Sweating Increased	1.1%	1.0%
PSYCHIATRIC DISORDERS		
Anxiety	1.1%	0.3%
Insomnia	1.2%	0.3%

*p≤0.05 for treatment differences †Includes vertigo

In these placebo-controlled studies of 665 CARDURA® patients, treated for a mean of 65 days, additional adverse reactions have been reported. These are less than 1% and not distinguishable from those that occurred in the placebo group. Adverse reactions with an incidence of less than 1% but of clinical interest are (CARDURA® vs. placebo): *Cardiovascular System:* angina pectoris (0.6% vs. 0.7%), postural hypotension (0.3% vs. 0.3%), syncope (0.5% vs. 0.0%), tachycardia (0.9% vs. 0.0%); *Urogenital System:* dysuria (0.5% vs. 1.3%), and *Psychiatric Disorders:* libido decreased (0.8% vs. 0.3%). The safety profile in patients treated for up to three years was similar to that in the placebo-controlled studies.

The majority of adverse experiences with CARDURA® were mild.

B. Hypertension

CARDURA® has been administered to approximately 4000 hypertensive patients, of whom 1879 were included in the hypertension clinical development program. In that program, minor adverse effects were frequent, but led to dis-

0.3%), tachycardia (0.3% vs 0.0%); *Urogenital System*: dysuria (0.5% vs 0.0%); and *Psychiatric Disorders*: libido decreased (0.8% vs 0.3%). The safety profile in patients treated for up to three years was similar to that in the placebo-controlled studies.

The majority of adverse experiences with CARDURA® were mild.

B. *Hypertension*

CARDURA® has been administered to approximately 4000 hypertensive patients, of whom 1679 were included in the hypertension clinical development program. In that program, minor adverse effects were frequent, but led to discontinuation of treatment in only 7% of patients. In placebo-controlled studies adverse effects occurred in 49% and 40% of patients in the doxazosin and placebo groups, respectively, and led to discontinuation in 2% of patients in each group. The major reasons for discontinuation were postural effects (2%), edema, malaise/fatigue, and some heart rate disturbance, each about 0.7%.

In controlled hypertension clinical trials directly comparing CARDURA® to placebo there was no significant difference in the incidence of side effects, except for dizziness (including postural), weight gain, somnolence and fatigue/malaise. Postural effects and edema appeared to be dose related. The prevalence rates presented below are based on combined data from placebo-controlled studies involving once daily administration of doxazosin at doses ranging from 1-16 mg. Table 4 summarizes those adverse experiences (possibly/probably related) reported for patients in these hypertension studies where the prevalence rate in the doxazosin group was at least 0.5% or where the reaction is of particular interest.

TABLE 4
ADVERSE REACTIONS DURING PLACEBO-CONTROLLED STUDIES

	HYPERTENSION	
	DOXAZOSIN (N=339)	PLACEBO (N=336)
CARDIOVASCULAR SYSTEM		
Dizziness	19%	9%
Vertigo	2%	1%
Postural Hypotension	0.3%	0%
Edema	4%	3%
Palpitation	2%	3%
Arrhythmia	1%	0%
Hypotension	1%	0%
Tachycardia	0.3%	1%
Peripheral Ischemia	0.3%	0%
SKIN & APPENDAGES		
Rash	1%	1%
Pruritus	1%	1%
MUSCULOSKELETAL SYSTEM		
Arthralgia/Arthritis	1%	0%
Muscle Weakness	1%	0%
Myalgia	1%	0%
CENTRAL & PERIPHERAL N.S.		
Headache	14%	16%
Paresthesia	1%	1%
Kinetic Disorders	1%	0%
Ataxia	1%	0%
Hypertonia	1%	0%
Muscle Cramps	1%	0%
AUTONOMIC		
Mouth Dry	2%	2%
Flushing	1%	0%
SPECIAL SENSES		
Vision Abnormal	2%	1%
Conjunctivitis/Eye Pain	1%	1%
Tinnitus	1%	0.3%
PSYCHIATRIC		
Somnolence	5%	1%
Nervousness	2%	2%
Depression	1%	1%
Insomnia	1%	1%
Sexual Dysfunction	2%	1%
GASTROINTESTINAL		
Nausea	3%	4%
Diarrhea	2%	3%
Constipation	1%	1%
Dyspepsia	1%	1%
Flatulence	1%	1%
Abdominal Pain	0%	2%
Vomiting	0%	1%
RESPIRATORY		
Rhinitis	3%	1%
Dyspnea	1%	1%
Epistaxis	1%	0%
URINARY		
Polyuria	2%	0%
Urinary Incontinence	1%	0%
Micturition Frequency	0%	2%
GENERAL		
Fatigue/Malaise	12%	6%
Chest Pain	2%	2%
Asthenia	1%	1%
Face Edema	1%	0%
Pain	2%	2%

Additional adverse reactions have been reported, but these are, in general, not distinguishable from symptoms that might have occurred in the absence of exposure to doxazosin. The following adverse reactions occurred with a frequency of between 0.5% and 1%: syncope, hypoesthesia, increased sweating, agitation, increased weight. The following additional adverse reactions were reported by <0.5% of 3960 patients who received doxazosin in controlled or open, short- or long-term clinical studies, including international studies. *Cardiovascular System*: angina pectoris, myocardial infarction, cerebrovascular accident; *Autonomic Nervous System*: pallor; *Metabolic*: thirst, gout, hypokalemia; *Hematopoietic*: lymphadenopathy, purpura; *Reproductive System*: breast pain; *Skin Disorders*: alopecia, dry skin, eczema; *Central Nervous System*: paresis, tremor, twitching, confusion, migraine, impaired concentration; *Psychiatric*: paroniria, amnesia, emotional lability, abnormal thinking, depersonalization; *Special Senses*: parosmia, earache, taste perversion, photophobia, abnormal lacrimation; *Gastrointestinal System*: increased appetite, anorexia, fecal incontinence, gastroenteritis; *Respiratory System*: bronchospasm, sinusitis, coughing, pharyngitis; *Urinary System*: renal calculus; *General Body System*: hot flushes, back pain, infection, fever/rigors, decreased weight, influenza-like symptoms.

CARDURA® has not been associated with any clinically significant changes in routine biochemical tests. No clinically relevant adverse effects were noted on serum potassium, serum glucose, uric acid, blood urea nitrogen, creatinine or liver function tests. CARDURA® has been associated with decreases in white blood cell counts (see PRECAUTIONS).

OVERDOSAGE

Experience with CARDURA® overdosage is limited. Two adolescents who each intentionally ingested 40 mg [illegible]

[illegible] anorexia, fecal incontinence, gastroenteritis; *Respiratory System:* bronchospasm, sinusitis, coughing, pharyngitis; *Urinary System:* renal calculus; *General Body System:* hot flushes, back pain, infection, fever/rigors, decreased weight, influenza-like symptoms.

CARDURA® has not been associated with any clinically significant changes in routine biochemical tests. No clinically relevant adverse effects were noted on serum potassium, serum glucose, uric acid, blood urea nitrogen, creatinine or liver function tests. CARDURA® has been associated with decreases in white blood cell counts (see PRECAUTIONS).

OVERDOSAGE

Experience with CARDURA® overdosage is limited. Two adolescents who each intentionally ingested 40 mg CARDURA® with diclofenac or salicylamide were treated with gastric lavage with activated charcoal and made full recoveries. A two-year-old child who accidently ingested 4 mg CARDURA® was treated with gastric lavage and remained normotensive during the five-hour emergency room observation period. A six-month-old child accidentally received a crushed 1 mg tablet of CARDURA® and was reported to have been drowsy. A 32-year-old female with chronic renal failure, epilepsy and depression intentionally ingested 60 mg CARDURA® (blood level 0.9 µg/mL; normal values in hypertensives≤0.02 µg/mL); death was attributed to a grand mal seizure resulting from hypotension. A 39-year-old female who ingested 70 mg CARDURA® alcohol and Dalmane® (flurazepam) developed hypotension which responded to fluid therapy.

The oral LD_{50} of doxazosin is greater than 1000 mg/kg in mice and rats. The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of fluid. As doxazosin is highly protein bound, dialysis would not be indicated.

DOSAGE AND ADMINISTRATION

DOSAGE MUST BE INDIVIDUALIZED. The initial dosage of CARDURA® in patients with hypertension and/or BPH is 1 mg given once daily in the a.m. or p.m. This starting dose is intended to minimize the frequency of postural hypotension and first dose syncope associated with CARDURA®. Postural effects are most likely to occur between 2 and 6 hours after a dose. Therefore blood pressure measurements should be taken during this time period after the first dose and with each increase in dose. If CARDURA® administration is discontinued for several days, therapy should be restarted using the initial dosing regimen.

A. ***BENIGN PROSTATIC HYPERPLASIA 1-8 mg once daily.*** The initial dosage of CARDURA® is 1 mg, given once daily in the a.m. or p.m. Depending on the individual patient's urodynamics and BPH symptomatology, dosage may then be increased to 2 mg and thereafter to 4 mg and 8 mg once daily, the maximum recommended dose for BPH. The recommended titration interval is 1-2 weeks. Blood pressure should be evaluated routinely in these patients.

B. ***HYPERTENSION 1-16 mg once daily.*** The initial dosage of CARDURA® is 1 mg given once daily. Depending on the individual patient's standing blood pressure response based on measurements taken at 2-6 hours post-dose and 24 hours post-dose), dosage may then be increased to 2 mg and thereafter if necessary to 4 mg, 8 mg and 16 mg to achieve the desired reduction in blood pressure. Increases in dose beyond 4 mg increase the likelihood of symptomatic postural effects including syncope, postural dizziness/vertigo and postural hypotension. At a titrated dose of 16 mg once daily the frequency of postural effects is about 12% compared to 3% for placebo.

HOW SUPPLIED

CARDURA® (doxazosin mesylate) is available as colored tablets for oral administration. Each tablet contains doxazosin mesylate equivalent to 1 mg (white), 2 mg (yellow), 4 mg (orange) or 8 mg (green) of the active constituent, doxazosin.

CARDURA® TABLETS (doxazosin mesylate) are available as 1 mg (white), 2 mg (yellow), 4 mg (orange) and 8 mg (green) scored tablets.

Bottles of 100: 1 mg (NDC 0049-2750-66)
2 mg (NDC 0049-2760-66)
4 mg (NDC 0049-2770-66)
8 mg (NDC 0049-2780-66)

Unit Dose Packages of 100: 1 mg (NDC 0049-2750-41)
2 mg (NDC 0049-2760-41)
4 mg (NDC 0049-2770-41)
8 mg (NDC 0049-2780-41)

Recommended Storage: Store below 86°F (30°C).

CAUTION: Federal law prohibits dispensing without prescription.

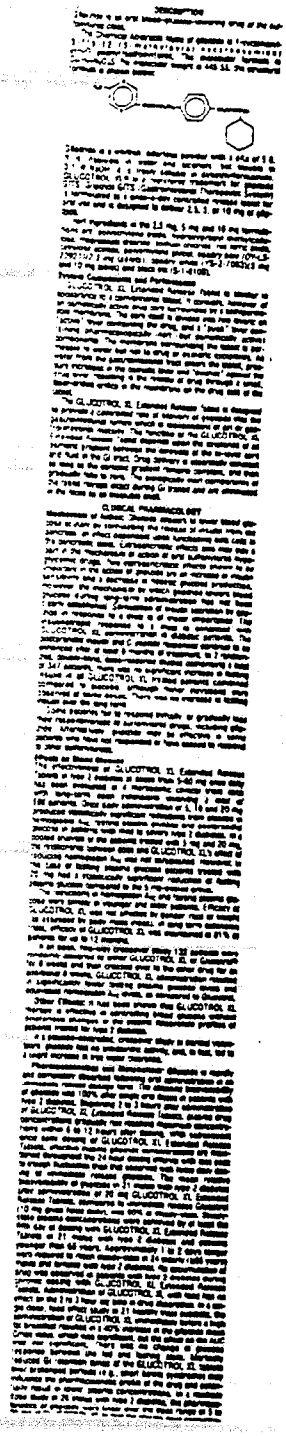
Pfizer Roerig
Division of Pfizer Inc, NY, NY 10017

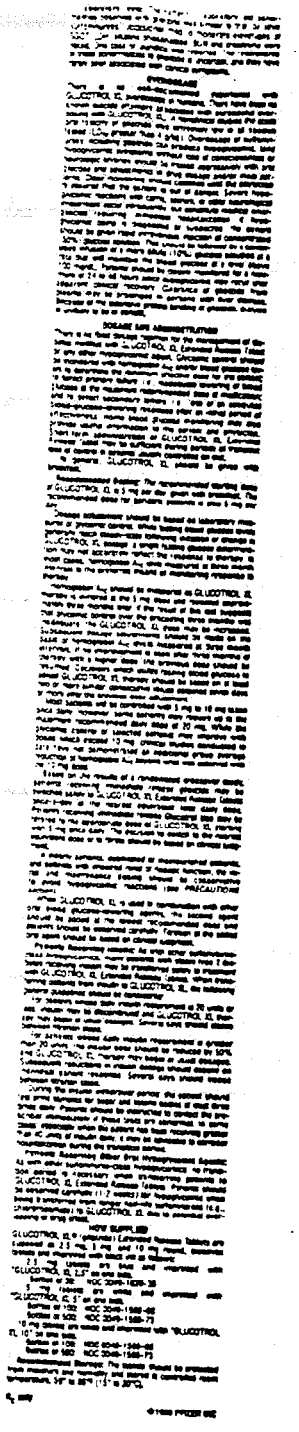
69-4538-00-6

Printed in U.S.A.
Revised June 1997

59-4952-00-5

GLUCOTROL XL®
(glipizide)
Extended Release Tablets





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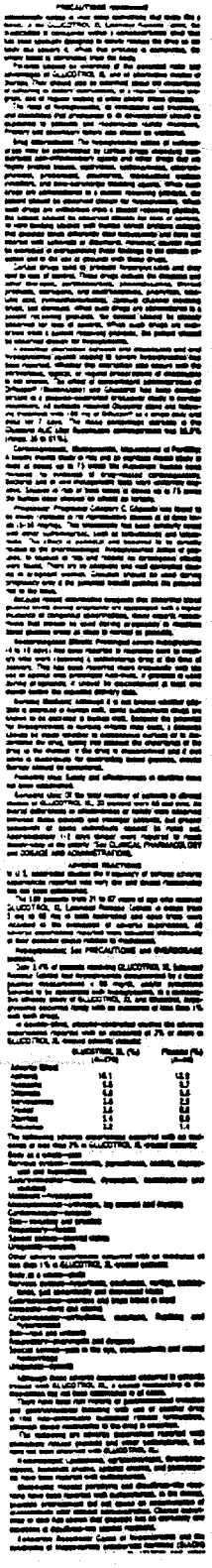
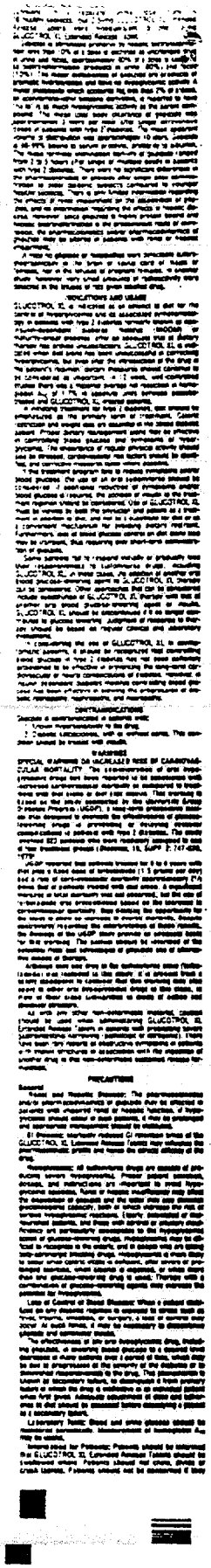




CONFIDENTIAL

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF NEW YORK

LAWRENCE D. BERNHARDT, Plaintiff, vs. PFIZER, INC., Defendant.	00 CIV 4042 (LMM)
ARNOLD LIEBMAN, Plaintiff, vs. PFIZER, INC., Defendant.	00 CIV 4379 (LMM)

November 6, 2000

1:55 p.m.

Deposition of JOSEPH M. FECZKO, held at the offices of Kaye, Scholer, Fierman, Hays & Handler, 425 Park Avenue, New York, New York, pursuant to Notice, before Cathi Irish, a Registered Professional Reporter and Notary Public of the State of New York.

A. Right.

Q. I want to look now at the page of the document now that ends 8752.

A. All right.

Q. Earlier I had asked you how significant Cardura was in terms of sales for PPG overall, and I was wondering if looking at this document would refresh your recollection as to what Cardura sales were in 1998 as compared to the other products of Pfizer.

MS. LESKIN: Objection. I believe the prior question referred to 1999 and not 1998.

MR. GRAZIANO: Okay, let me redo it and make it easier.

Q. This page of Exhibit 2, 8752 appears to list seven products and it shows Cardura with sales of 685 million right under Viagra with sales of 784 million in 1998.

As far as you know, is this page of the document accurate?

MS. LESKIN: If you know.

A. As far as I know it is.

Q. As far as you know in 1998, was Cardura

discussions about the label.

This is what's required of our sales representatives. If they get questions outside the label, if it's within the approved document that we've given them they can address it. However, if it's outside that document, then they have to refer to medical information.

This is in a sense standard because our representatives are under strict actually guidances and there are strict advertising principles set down by the FDA about what they can and cannot say about any drug outside the label.

Q. So at this point Pfizer's representatives are not volunteering any information about ALLHAT to physicians unless they first receive a request from the physicians; is that right?

MS. LESKIN: Objection to the extent it misstates testimony.

MR. GRAZIANO: You can answer.

A. The representatives to the best of my knowledge are not proactively discussing ALLHAT.

Q. Have there been other situations in the past where Pfizer's representatives were asked to

A. We are always examining our drugs.

Q. Is that a yes?

A. We continue --

MS. LESKIN: Asked and answered. He doesn't have to give you the answer you want. If he can answer it yes or no, he will but he's already --

Q. You realize you may be testifying before a judge in this case shortly?

A. Yes.

Q. If I were to ask you in front of the judge yes or no is Pfizer still trying to determine if Cardura has a negative effect in some patients, would you be able to answer the question yes or no?

MS. LESKIN: Objection argumentative.

A. We are always looking for safety signals. We have done this right now and we will continue to look and examine. In the sense we are continuing to look because we are asking the NHLBI for additional data. We want to understand this better. We think there's a good explanation for this finding but we don't have the data and we will continue to look for this data.

Q. So at this point there is a possibility

has been issued by Pfizer?

A. That's correct, there's no warning letter.

Q. At the same time is it fair to say that Pfizer has been proactive in communicating with physicians that the study doesn't show that Cardura is harmful?

MS. LESKIN: Objection, vague.

MR. GRAZIANO: You can answer.

MS. LESKIN: If you know.

A. I don't know the context of the actual meetings with the key experts. I do know that members of the ALLHAT committee are frequently and have been at -- ALLHAT steering committee have been at some of these meetings and the discussions have revolved around the actual ALLHAT article.

What conclusions are discussed or what course the decision goes at these meetings, I have not attended any of them but these are sort of free exchange, scientific discussions amongst physicians and these are -- in past experience, physicians are very willing to express their own opinions what they think is going on.

Q. Putting the physicians aside, are you

these standardized responses before?

A. I have not, no.

Q. Are you aware that physicians may -- it's possible that physicians are being told by the Pfizer sales force that quote, "Cardura is an exceptionally safe drug"?

MS. LESKIN: Objection, assumes facts not in evidence.

MR. GRAZIANO: I'm only asking if you're aware of that.

A. I would like to read this for a second because I haven't seen this before.

Q. Sure.

Have you looked at the document?

A. Yes, I have.

Q. So my question to you was not if you were aware of these specific responses in this document but are you aware that sales representatives are informing physicians that's Cardura is an exceptionally safe drug?

MS. LESKIN: Objection, assumes facts not in evidence.

A. I don't know exactly what they are telling physicians but these appear to be from

CARDURA ALLHAT PREPARATION PLAN

Cardura is one of the Magnificient 7 products that counts for significant revenue and profit for Pfizer Europe. Our analysis of the available information from New York regarding the recent decision to suspend the doxasozin treatment arm of the ALLHAT study has highlighted both **potential threats** to our business, as well as a list of **proactive steps** needed to address these issues.

POTENTIAL THREATS

ALLHAT information, in the form of the Investigator letter, ACC abstract, NEJM article:

- In the hands of our competitors are long awaited tools to focus on Cardura as sub optimal choice for treating hypertensive patients over 55.
- In the hands of our governments are useful for requesting labeling or price changes, not to mention the risk of creating a call for European label harmonization
- In the hands of the press can be used to disseminate "panic" among current patients
- In the hands of our FF--without proper preparation and the appropriate perspective on the issue (one study, albeit well-designed and run, vs. 3.4 billion patient days worldwide and more than 10 years on the market)—will risk losing motivation and creating a defensive position

PROACTIVE STEPS REQUESTED

Countries will need to have on hand documentation **NO LATER THAN MARCH 1**. This will be used in coordination between all European countries and only in the case of need, but will allow all to be able to answer a series of questions from any of the above mentioned sources of threat.

- Copies as soon as possible of Investigator letter, ACC abstract, and NEJM article
- An immediate and proactive plan to seek ACC support for a LIVE perspective to the ALLHAT presentation, perhaps with a debate format. Note that many countries will have customers attending ACC, which always draws a large non-US attendance
- An extensive data analysis—both of published and inhouse data—of the safety databases to date for Cardura
- A complete review of ongoing large trial, eg AASK, that have yet to show any issues regarding Cardura
- A position to explain any difference in the use of standard vs. GITS related to this issue
- A "Hub-and-Spoke" system of priority alerts for any issues arising via the media, with the appropriate Q&A prepared

Countries will continue to analyze their source of Cardura business (HTN or BPH; monotherapy vs. combination) and plan the appropriate contingency as the process moves forward. It is essential that each market be able to inform their key opinion leaders and Field Forces in time to be ready, if not proactive, vs. our competition! We cannot allow the Norvasc ABCD/FACET situation to repeat itself again.

U.S. Pharmaceuticals Group
Pfizer Inc
235 East 4 Street
New York, N Y 10017-5755

Pfizer

U.S. Pharmaceuticals

Rec'd 2/17/00
(@ 6701 Rockledge)

February 10, 2000

Peter L. Frommer, MD
Deputy Director
Department of Health & Human Services
Public Health Service
National Institute of Health
9000 Rockville Pike
Building #31 - Room 5A49
Bethesda, Maryland 20892

Dear Peter,

I am enclosing copies of the charts looking at Cardura/alpha-blocker use that you requested last week. As you see, Cardura comprises almost 3% of the total worldwide antihypertensive market. Although this seems like a small percentage, it is a vast market, and Cardura sales approach $800,000,000 worldwide. For worldwide sales, Cardura ranks in 7th place amongst branded antihypertensives, 11th in the USA. The majority of our use is in hypertension – in the USA, about half is hypertension alone, a quarter hypertension with concomitant BPH, and the final quarter, BPH alone. Also, the majority of Cardura use in hypertension is as add-on or combination therapy. As you see, Cardura represents an important cardiovascular product for us.

I would like to thank you, and your colleagues at NIH and CTC for giving us an advance look at the data, and for notifying us of the decision prior to the Steering Committee meeting. I also appreciate your taking note of our concerns regarding our need for advance copies of your materials, in order that we may prepare our responses to questions that will inevitably arise from the medical community and from patients as soon as the information becomes public. It is urgent that we have access to these materials soon to prepare coordinated responses. May I ask if you would kindly let us know when we might anticipate receiving them? We are concerned that as soon as patients start receiving notification – which I believe could be as early as the end of next week – and go to their primary care givers, we might anticipate questions, and we need to be prepared. Any information we are given will, of course, be treated confidentially until it is officially made public by NIH.

I have sent Barry a list of questions regarding the data, so we might understand the results as fully as possible.

We are also looking forward to receiving a copy of the paper as soon as possible. While we appreciate the need for you to discuss the data in a scientific forum such as the ACC, we have other responsibilities as well. As a company that strives to maintain the highest ethical standards, we do not want to market a product that either causes harm or even fails to provide benefit. From what we have heard, we do not believe this to be the case with doxazosin (especially as most is used as add-on/combination). However, I cannot stress too strongly our need to evaluate the situation as fully as possible as soon as possible.

We greatly appreciate your help in providing us with the information requested.

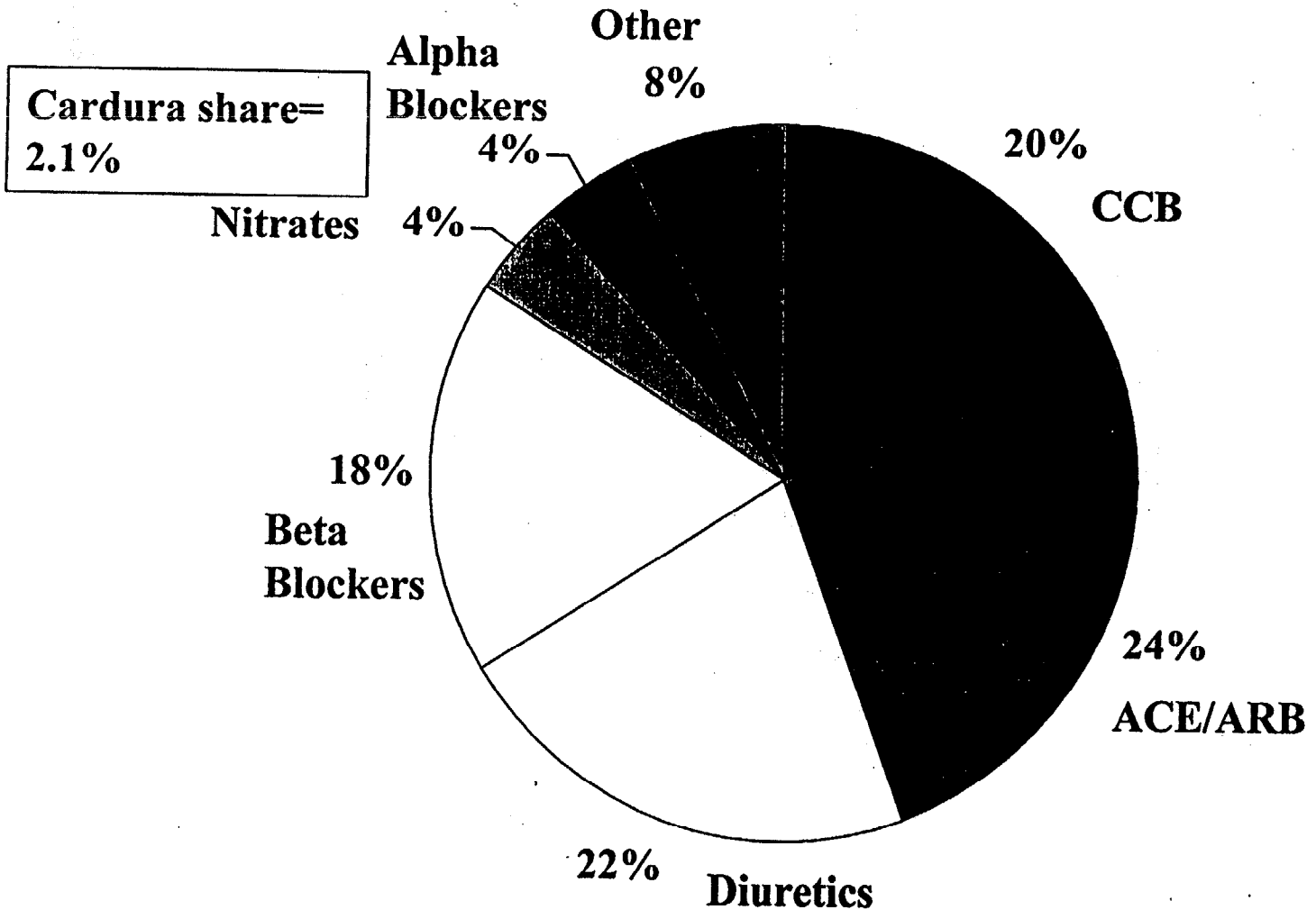
With warm regards,

Yours sincerely,

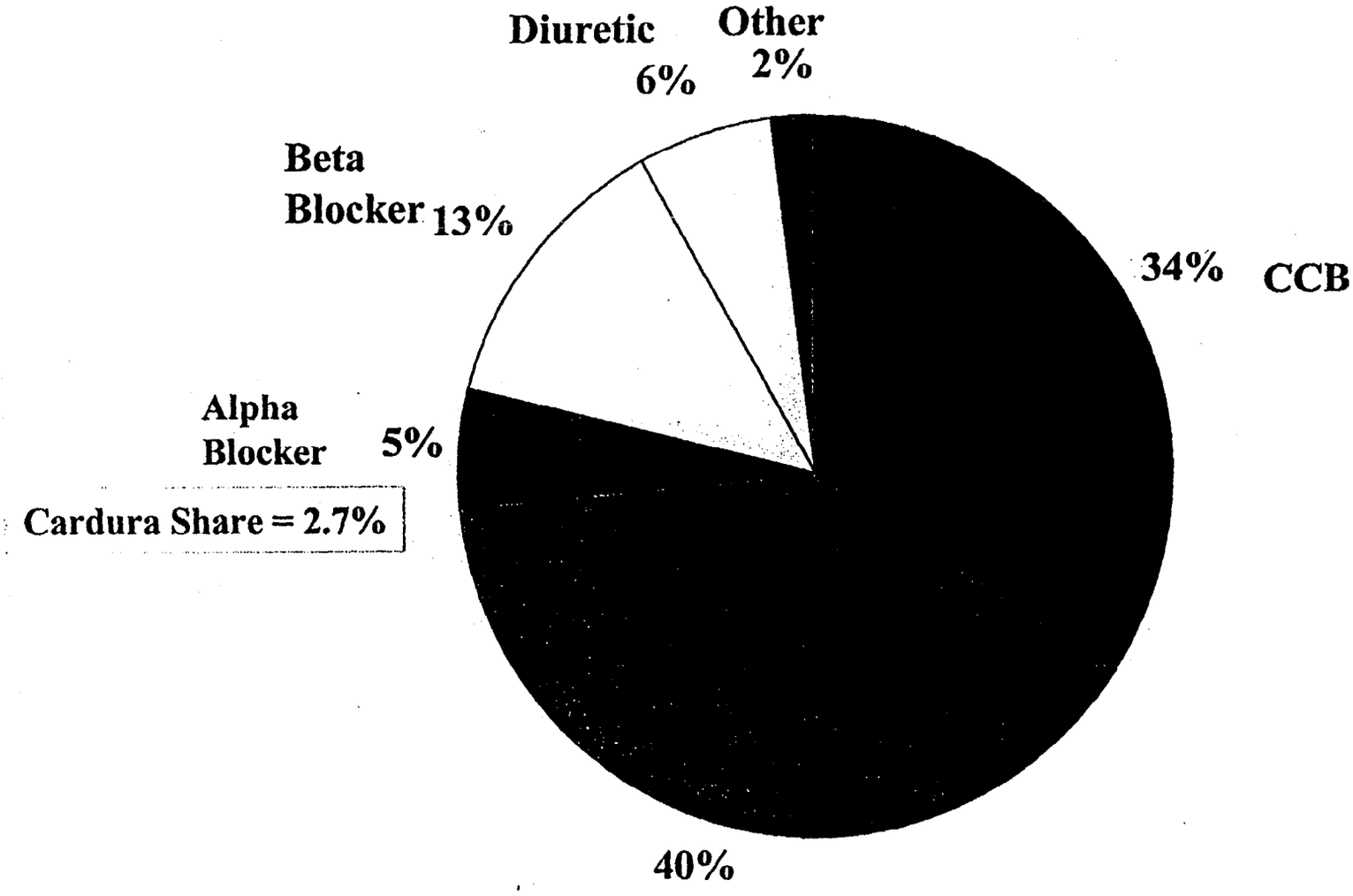
Patricia A. Walmsley, MB, FRCPath
Senior Associate Medical Director

cc Dr Jeff Cutler

US Hypertension Market

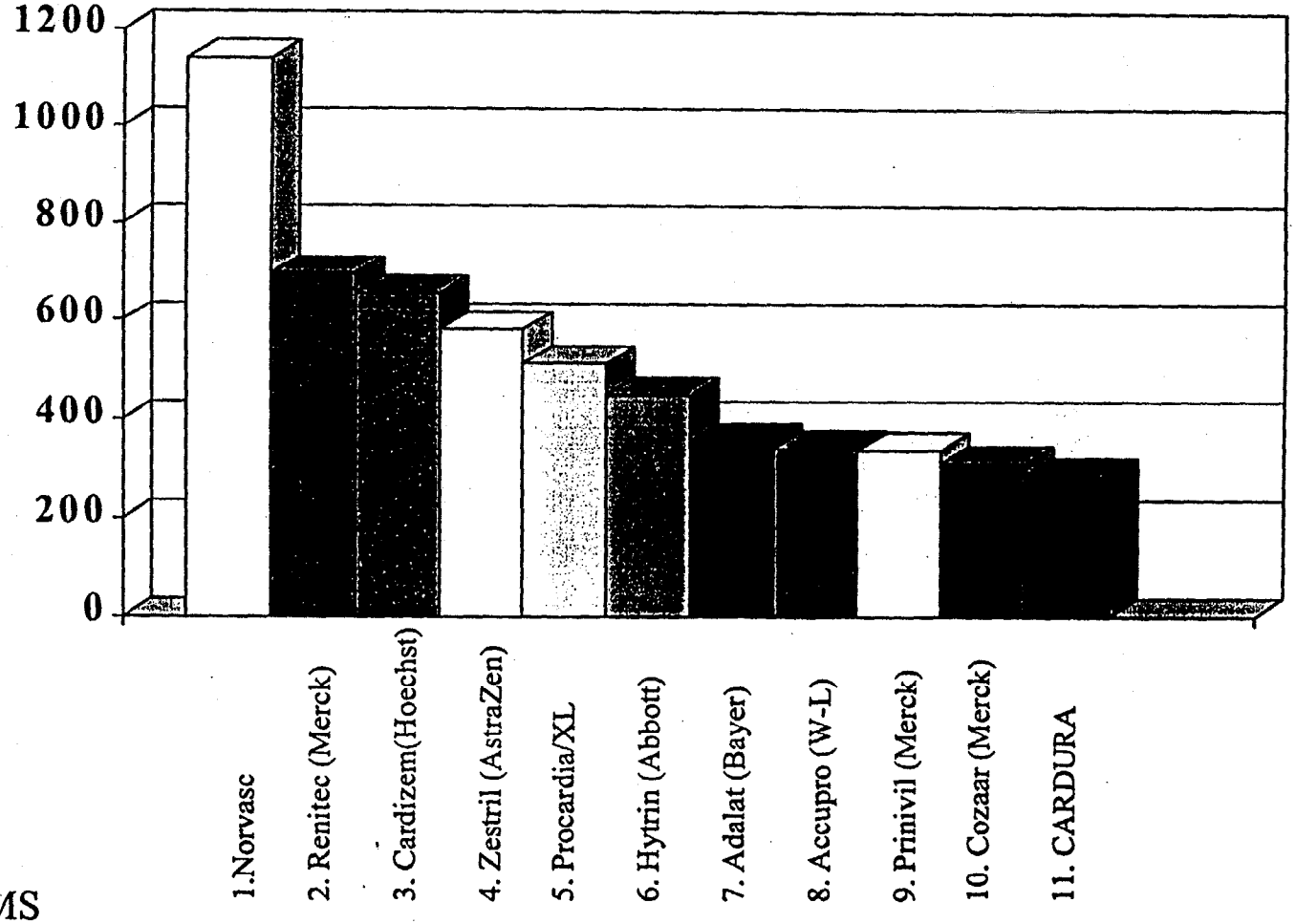


Worldwide Antihypertensive Market



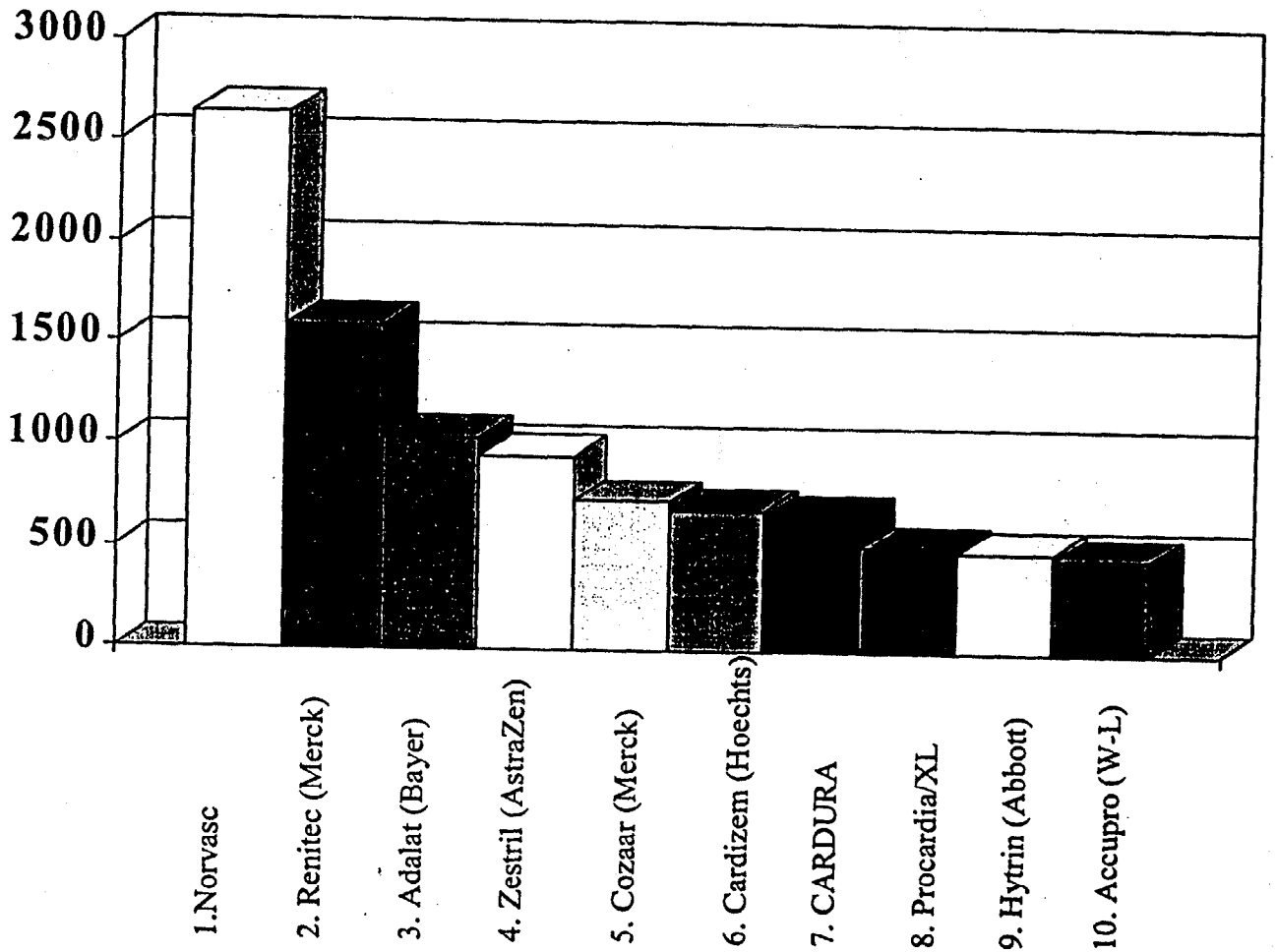
Source: IMS Midas

US Hypertension Market



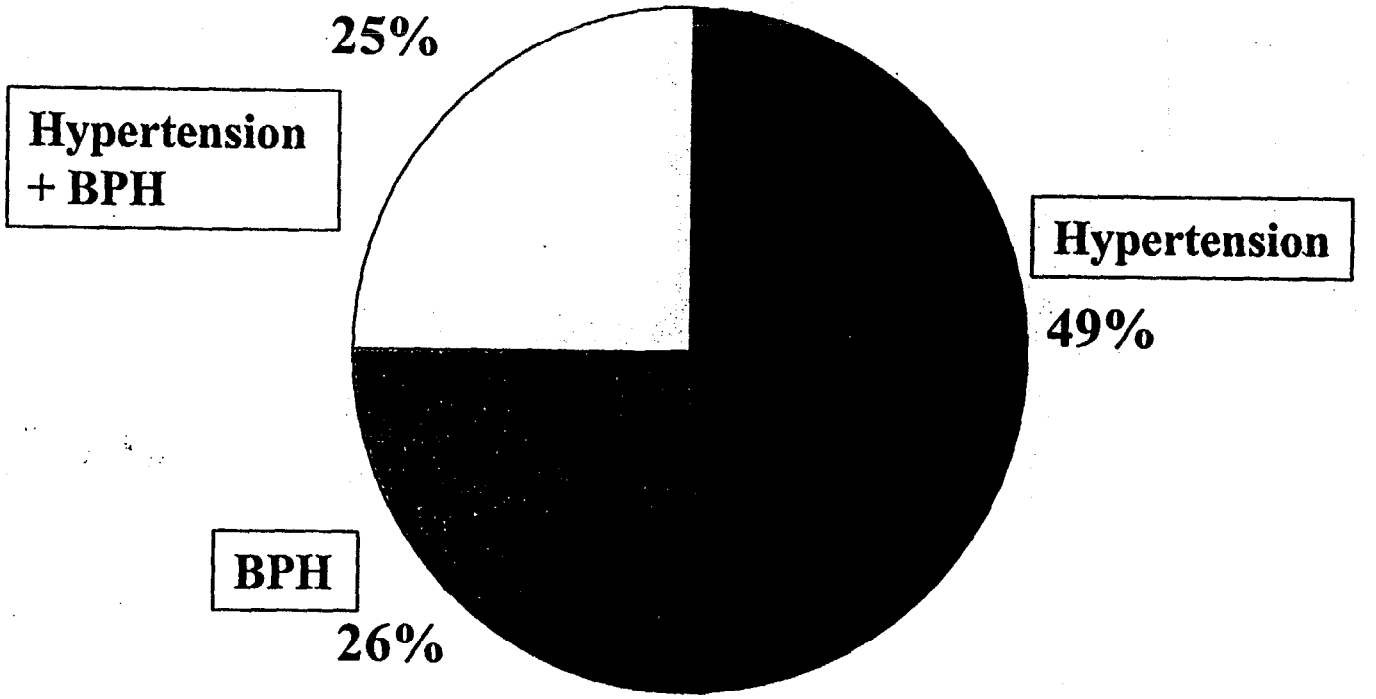
Source: IMS

Worldwide Hypertension Market

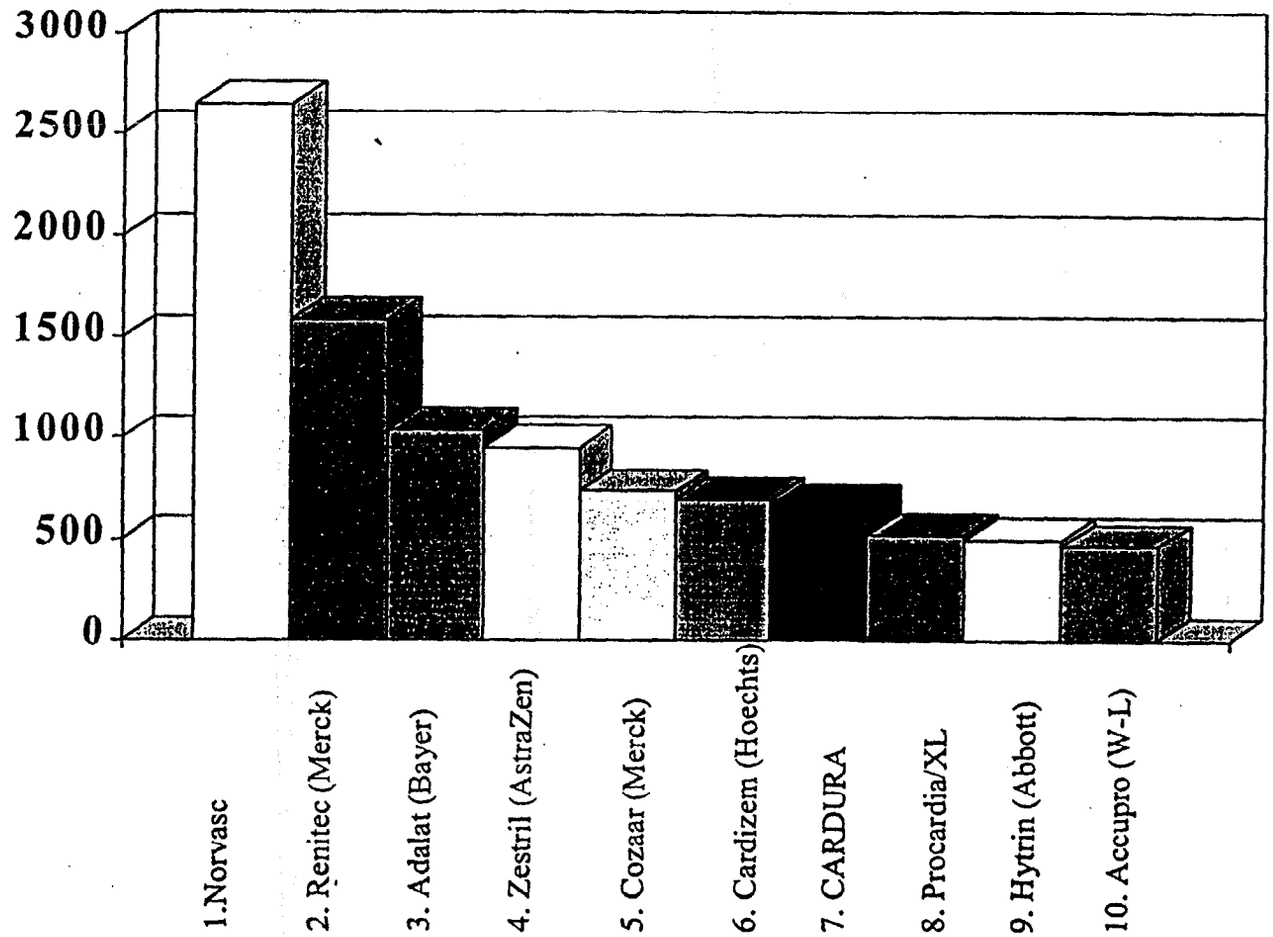


Source: IMS

US Cardura Usage



Worldwide Hypertension Market



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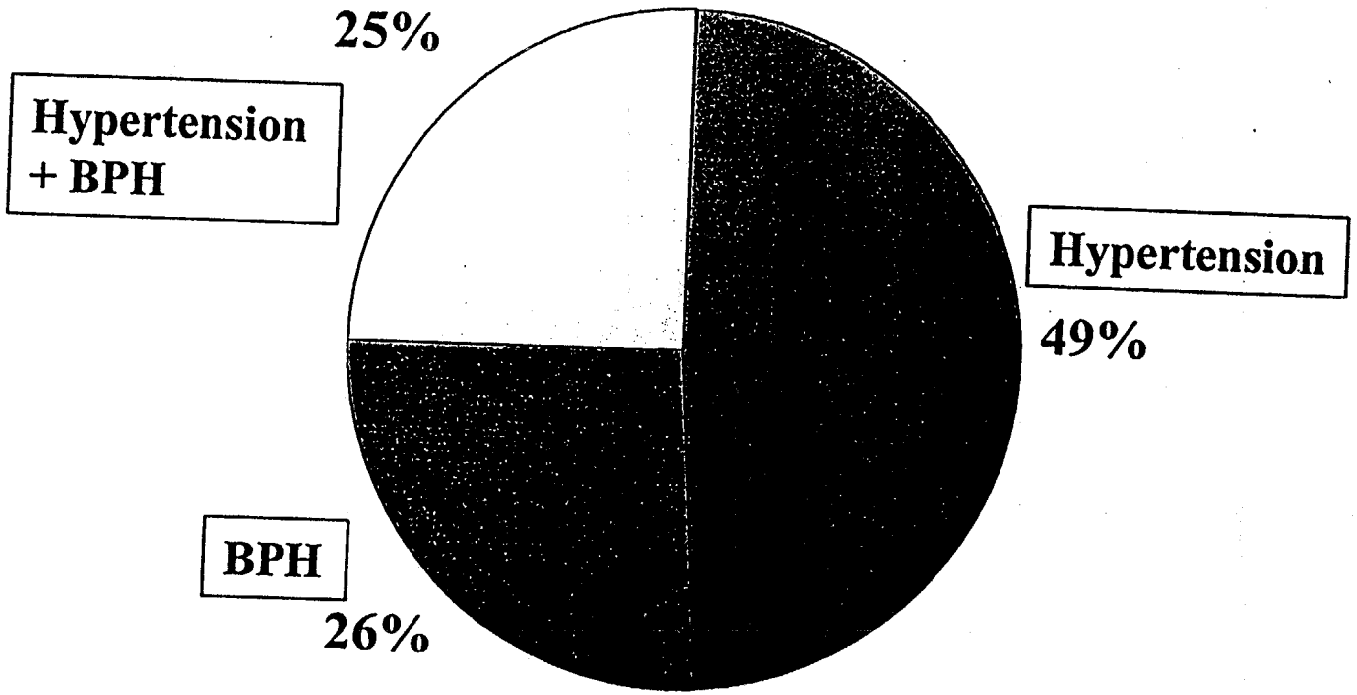
US Cardura Usage



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Volume 14 Number 5 May 2000

In this issue

Journal of Human Hypertension (2000) 14, 287–289

www.nature.com/jhh

COMMENTARY

Do alpha blockers cause heart failure and stroke? Observations from ALLHAT

DG Beevers and GYH Lip
University Department of Medicine, City Hospital, Birmingham, UK

Keywords: alpha blockers; heart failure; strokes

The Antihypertensive and Lipid Lowering treatment to prevent Heart Attack Trial (ALLHAT) is one of two current mega-trials (the other being the Anglo-Scandinavian Cardiac Outcomes Study, ASCOT), with over 42 000 'high-risk' antihypertensive patients with two objectives: firstly, to assess whether the newer antihypertensive agents (amlodipine, lisinopril, and doxazosin) reduce the incidence of coronary artery disease (CAD) when compared with a diuretic (chlorthalidone); and secondly, whether statin therapy in hypertensive patients with moderate hypercholesterolaemia will reduce cardiac events compared with placebo. Patients were randomised to one of the above four antihypertensive agents, with a planned follow-up of 4–8 years.[1]

On 24 January, 2000, the independent review committee recommended termination of the doxazosin arm on account of a 25% higher rate of the combined cardiovascular disease (CVD), a major secondary end-point, when compared to the patients taking chlorthalidone.[2]

The interim results were presented in March 2000 at the American College of Cardiology meeting in Anaheim, California, by Dr Barry Davis. The patients in both the doxazosin arm (n = 9067) and the chlorthalidone group (n = 15268) were very similar for baseline characteristics, and at 4 years, 86% of patients randomised to chlorthalidone were still taking the drug (*vs* 75% in the doxazosin arm). At 4 years, the mean systolic blood pressure was 135 mm Hg in the chlorthalidone group and 137 mm Hg in the doxazosin arm, with similar mean diastolic blood pressures. There was no difference in the relative risk (RR) of CAD between patients receiving doxazosin and those receiving chlorthalidone (RR 1.03; 95% CI 0.9–1.17), but the relative risk of combined CVD in the doxazosin arm compared with the chlorthalidone arm was 1.25 (95% CI 1.17–1.33; $P <$ 0.0001), with the event curves diverging early. This effect was mainly related to an increased relative risk of heart failure in the patients taking doxazosin, of 2.04 (95% CI 1.79–2.32), which was seen across gender, age, and ethnic subgroups. The relative risk for stroke was also increased in the doxazosin group (RR 1.19 (95% CI 1.01–1.14; P = 0.04)). Chlorthalidone, which is a much cheaper drug, therefore appeared superior to doxazosin for hypertension control, drug compliance, and reduction of cardiovascular complications.

Whilst the alpha blockers have been available for a great many years they have never been subjected to a long-term outcome trial in hypertension. In the short-term they seem attractive because not only do they lower blood pressure but they also have mildly beneficial effects on plasma lipid levels and also appear to improve insulin sensitivity.[3] The early alpha blocker, prazocin, was not popular because of a rapid first dose effect sometimes causing postural hypotension. Furthermore, it had to be given three times per day.[4] The arrival of doxazosin and its competitor terazosin seemed to be a major breakthrough.[5] Because of the lack of long-term outcome data of the use of doxazosin at first-line therapy, it is always tended to be a drug used in reserve for patients whose blood pressures are resistant to other therapies. For example in the ASCOT trial doxazosin is the third-line drug to add-in to either atenolol with bendrofluazide or perindopril with amlodipine.[6] There are also favourable reports of the use of doxazosin together with the angiotensin-converting enzyme (ACE) inhibitors.[7]

The adverse effects of doxazosin appear until now to be related to symptomatic side-effects. The presence of alpha receptors at the bladder neck leads to relaxation of the urethra. This is a beneficial effect in men as it relieves the symptoms of benign prostatic hypertrophy.[8] Alpha blockers have already been used for this condition even in people who do not have high blood pressure. The effect however on the alpha-receptors in the bladder neck is disadvantageous in women and may lead to stress or urge incontinence.[9] Very occasionally patients do complain of what sounds like first dose hypotension and for that reason doxazosin is still often started with the first few doses to be taken at night. This precaution was absolutely necessary for patients receiv-

Correspondence: Prof DG Beevers
Received and accepted 24 March 2000

ing prazosin but was hoped it would be less necessary for patients on doxazosin. The arrival of a longer acting gastrointestinal transfer system (GITS) formulation of doxazosin 8 mg was awaited with interest.

The adverse findings in the ALLHAT study must be looked at with caution at this stage. Clearly more information will become available. Indeed, the antihypertensive effect of doxazosin appears to be as good as that with the comparator drugs. In the Treatment of Mild Hypertension Study (TOMHS) doxazosin was equally effective as chlorthalidone, and had similar effects on echocardiographic left ventricular size.[10] In time we will perhaps learn whether the patients who were randomised to receive doxazosin in ALLHAT differed in any way from those randomised to the other drugs in respect of important baseline parameters such as left ventricular size or function.

Assuming that the adverse effects of doxazosin in ALLHAT are not due to confounding variables or systematic sources of bias, the next question is whether this adverse effect sounds plausible. What might the mechanisms be? In the past alpha blockers were considered as possible drugs for the treatment of heart failure and were not thought to be likely to cause it or to make it worse.[11] Whilst the difference between prazosin and placebo was not statistically significant, close examination of data on 642 men from the Vasodilator-Heart Failure Trial-1 (VeHFT-I) revealed 91 deaths (49.7%) in the prazosin group, compared to 120 deaths (44.0%) in those on placebo and 72 deaths (38.7%) in the hydralazine-nitrate group.[11] By reducing peripheral vascular resistance, the alpha-receptor blockers should reduce left ventricular after-load and therefore have effects which are beneficial and somewhat similar to those seen with ACE inhibitors or hydralazine with nitrates.[12] Short-term studies suggested that alpha blockers might have beneficial haemodynamic effects in patients with heart failure.[13–15] These findings however were mainly confined to patients receiving prazosin and not doxazosin.

It is generally considered that doxazosin has neutral effects on the renin-angiotensin system and does not cause any activation or suppression.[16] In that respect alpha blockers might seem more rather than less attractive than chlorthalidone which can cause a small shrinkage in plasma volume associated with a rise in plasma renin levels.

Clearly the doxazosin 'crisis' will be a source of much discussion in the coming months. We must be careful not to overreact. This is only one study showing this effect, albeit with tight confidence intervals, and it is possible that it might not be confirmed in future work. Secondly, it is possible that this might be a chance observation, although the 25% increase in relative risk of combined CVD in the doxazosin arm with a P value of <0.0001 seems convincing. We must not lose sight of the fact that in the ELITE I study losartan appeared to be better than captopril (although with a P value of only 0.035), but this was simply not confirmed in the much larger ELITE II study, which was presented at the American Heart Association meeting in November 1999.[17] It will be interesting to see whether the guidelines committees of the various National and International Hypertension Societies will modify their recommendations that alpha blockers can be used for first-line therapy.[18] It is certainly doubtful whether the alpha blockers should cease to be used as 'add-in' drugs where the first-line therapies have failed, because the hazards of uncontrolled hypertension may well override the possible hazard of alpha-blocking drugs.

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EMBARGOED UNTIL
Office
March 8, 2000

CONTACT: NHLBI Communications

(301) 496-4236

NHLBI Stops Part Of Study-

High Blood Pressure Drug Performs No Better Than Standard Treatment

The National Heart, Lung, and Blood Institute (NHLBI) has stopped one part of a large high blood pressure study early because one of the tested drugs, an alpha-adrenergic blocker, was found less effective than the more traditional diuretic in reducing some forms of cardiovascular disease.

Called ALLHAT-for Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial-the main portion of the study is comparing newer drug treatments for high blood pressure with a more conventional and less costly treatment. Another portion is comparing treatments for elevated cholesterol.

The NHLBI acted after an independent data review by an advisory committee. Patients were informed as soon as possible thereafter. Those on the alpha-adrenergic blocker were being offered an alternate medication, in consultation with their ALLHAT or personal physician.

The alpha-adrenergic blocker is doxazosin; the diuretic is chlorthalidone. Users of doxazosin had 25 percent more cardiovascular events and were twice as likely to be hospitalized for congestive heart failure as users of chlorthalidone. The drugs were similarly effective in preventing heart attacks and in reducing the risk of death from all causes.

Of the approximately 24 million Americans who take medication to treat their hypertension, about 1 million use an alpha blocker. Doxazosin, the alpha blocker used in ALLHAT, is sold under the brand name CarduraR. (Other alpha blockers used for hypertension are terazosin, sold under the brand name Hytrin, and prazosin, sold under the brand name Minipres).

"This finding adds important information to our understanding of antihypertensive drugs," said NHLBI Director Dr. Claude Lenfant. "No large-scale blood pressure treatment study had ever compared these two classes of drugs. Earlier studies were small and could not, for example, detect an increase in patients' risk of congestive heart failure."

The rest of the ALLHAT study, which began in 1994, will continue as scheduled and is expected to end in 2002.

ALLHAT involves 42,448 patients, enrolled through 623 clinics and centers across the United States, Canada, Puerto Rico, and the US Virgin Islands. About 7,000 U.S. veterans are participating through 69 Department of Veterans

Affairs clinics.

ALLHAT participants are aged 55 or older. Forty-seven percent are women, 47 percent are white, 35 percent are African American, and 16 percent are Hispanic, while 36 percent have diabetes.

On enrollment in the study, participants had been diagnosed with systolic and/or diastolic hypertension (140 mm Hg or higher and 90 mm Hg or higher, respectively), and had at least one added risk factor for coronary heart disease, such as diabetes, cigarette smoking, and a low level of high-density lipoprotein (HDL cholesterol), or had a history of (but no recent) heart attack or stroke.

ALLHAT participants receive periodic checkups and currently have between 2 and 6 years of followup.

ALLHAT also is comparing chlorthalidone with two other high blood pressure drugs-a calcium antagonist, called amlodipine, and an angiotensin-converting enzyme (ACE) inhibitor, called lisinopril.

About a quarter of ALLHAT's hypertensive patients also are participating in the cholesterol-lowering portion of the study. This includes a fourth of the patients on doxazosin, who will be able to continue their involvement in this aspect of the study.

The cholesterol-lowering study involves older patients with slightly to moderately elevated cholesterol. It is testing whether treatment with dietary changes and an HMG CoA reductase inhibitor, called pravastatin, reduces deaths from all causes better than dietary changes alone.

Other findings about doxazosin in comparison to chlorthalidone are:

Those in the doxazosin group had slightly higher systolic blood pressures than the chlorthalidone group, although the diastolic pressures were the same.

The doxazosin group also had poorer compliance with treatment-only 75 percent were still on the drug or another alpha blocker after 4 years, compared with 86 percent still taking chlorthalidone or another diuretic.

Due to the finding, NHLBI advises high blood pressure patients who now take an alpha-adrenergic blocker drug to consult with their doctors about a possible alternative. If a patient is just starting drug treatment, an alpha-adrenergic blocker may not be the best choice for initial therapy.

"Patients on an alpha blocker for high blood pressure should see their doctor and not just stop taking it," emphasized Dr. Jeffrey Cutler, director of the NHLBI Clinical Applications and Prevention Program and ALLHAT project officer. "We cannot conclude that the drug was harmful. Rather it didn't work as well as the diuretic in reducing cardiovascular disease."

About 50 million Americans have high blood pressure and about 52 million have high blood cholesterol. Both conditions are major risk factors for coronary heart disease and both strike particularly hard at older adults. High blood pressure

also is the chief risk factor for both congestive heart failure and stroke.

Treatment for both high blood pressure and high blood cholesterol typically starts with lifestyle changes, including increased physical activity and weight loss for the overweight. A healthy, low-saturated fat, low-cholesterol eating plan is advised and, for high blood pressure, avoiding excess salt, sodium, and alcohol.

When those changes do not lower elevated blood pressure or cholesterol enough, then drug therapy is needed.

For an interview about ALLHAT, contact the NHLBI Communications Office at (301) 496-4236.

NHLBI press releases, fact sheets, and other materials are available online at

www.nhbli.nih.gov

3/7/00

ALLHAT

February 16, 2000

Dear ALLHAT Investigator:

We are writing to provide important information concerning the Antihypertensive and Lipid-Lowering Therapy to Prevent Heart Attack Trial (ALLHAT), which has led to a modification of the protocol. This information is not public at this time and we ask that you keep this confidential until the patients in ALLHAT are informed and the NHLBI publicly releases the results. You should, however, send a copy of this letter to your IRB right away.

Following a review in January, the Director of the National, Heart, Lung, and Blood Institute accepted the recommendation of an independent data review committee. Accordingly, the doxazosin arm is being terminated. The recommendation was based on a very low probability of finding a favorable outcome for the group assigned to doxazosin compared to those assigned to chlorthalidone in the primary end-point (non-fatal myocardial infarction or coronary heart disease [CHD] death), coupled with a statistically significant 25 per cent higher rate of a secondary endpoint, combined cardiovascular disease (CVD). The higher rate of combined CVD (which includes the primary CHD end-point, angina pectoris, coronary revascularization, congestive heart failure (CHF), stroke, and peripheral arterial disease) was driven by a highly significant two-fold higher rate of CHF compared with the diuretic arm, but there were trends in the same direction for stroke and some other components. The primary CHD outcome, and total mortality were not different between the doxazosin and chlorthalidone arms.

It was determined that participants assigned to doxazosin should be informed of their BP treatment assignment and that the major clinical findings regarding this treatment and its comparison agent, chlorthalidone, be reported as soon as possible. Regarding other comparisons, the DSMB emphasized the crucial importance of continuing the rest of the BP and lipid-lowering components.

In order to communicate appropriate messages about the implications of these results for various participant groups, the Steering Committee has prepared letters and closeout materials for you to use to contact all your ALLHAT patients. The letters, the closeout forms, and the details on what procedures to follow will be provided to you within the next two weeks. Only those patients assigned to doxazosin and not in the lipid-lowering trial will be closed out. All other patients will be asked to continue, as the other questions ALLHAT is addressing remain unanswered. Those patients assigned to doxazosin and in the lipid-lowering trial portion of ALLHAT will be offered the use of open-label chlorthalidone, which the study will provide at no cost. All of this will be explained in the material you are to receive. If you have any questions, please contact your Regional Coordinator.

All of us who are conducting ALLHAT greatly appreciate your continued participation as a site principal investigator. You and your patients have already helped to answer one of the questions for which ALLHAT was designed. ALLHAT will continue, since the other questions to be answered by ALLHAT remain of fundamental importance for hypertension treatment. As detailed information is reported to the scientific and wider community, we will keep you fully informed.

Thank you for all your efforts to date and for your continuing diligent participation in ALLHAT.

Sincerely,

Curt Furberg, MD
Steering Committee Chair

Jackson Wright, MD, PhD
Steering Committee Vice-Chair

Jeffrey Cutler, MD, MPH
ALLHAT Project Director
National Heart, Lung, and Blood Institute

Barry Davis, MD, PhD
ALLHAT Clinical Trials Center
Principal Investigator and Director

PARTICIPANTS ASSIGNED TO DOXAZOSIN AND NOT IN LIPID COMPONENT
Revised 2/2/00

(Date)

Dear (patient name):

You have been participating in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). I am writing to let you know that ALLHAT is about to release its first results.

The purpose of the ALLHAT trial is to compare the ability of four commonly-used blood pressure medications to reduce the risk of heart disease, stroke, and early death. All four of the ALLHAT medicines were selected because they are commonly used by doctors when treating patients with high blood pressure and because doctors do not agree on which of the four is better.

When you joined ALLHAT, you were assigned by chance to take one of the four blood pressure medicines. Your safety has been monitored closely throughout the study by an independent panel of experts. During the most recent review, it was determined that the medicine to which you were assigned (doxazosin) appears to be the least effective of the four in preventing heart failure. Although heart failure was not the main focus of the study, the study reviewers have decided that the difference is important enough to notify me, and for me to notify you.

It is very important that we meet together to decide on a treatment for your high blood pressure, discuss what the study results mean for you, and to answer questions that you have. This will be your last ALLHAT visit. Please call my clinic by the end of March at the number listed below to make an appointment. DO NOT STOP TAKING YOUR ALLHAT MEDICINE UNTIL WE DECIDE ON THE BEST TREATMENT FOR YOU, BECAUSE THE MEDICINE IS HELPING TO KEEP YOUR BLOOD PRESSURE CONTROLLED. Be sure to bring your ALLHAT medicine to the clinic with you.

All of us who are conducting ALLHAT greatly appreciate your participation, which has helped the study to find out that one of the blood pressure medicines is less effective than the others at preventing heart failure. We still do not know which of the other ALLHAT medicines are best for treating high blood pressure.

Sincerely,

Address
Phone

Center and site #

PARTICIPANTS ASSIGNED TO DOXAZOSIN AND IN LIPID COMPONENT - PRAVASTATIN
Revised 2/2/00

(Date)

Dear (patient name):

You have been participating in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). I am writing to let you know that ALLHAT is about to release its first results.

The purpose of the ALLHAT trial is to compare the ability of four commonly-used blood pressure medications to reduce the risk of heart disease, stroke, and early death. All four of the ALLHAT medicines were selected because they are commonly used by doctors when treating patients with high blood pressure and because doctors do not agree on which of the four is better.

When you joined ALLHAT, you were assigned by chance to take one of the four blood pressure medicines. Your safety has been monitored closely throughout the study by an independent panel of experts. During the most recent review, it was determined that the medicine to which you were assigned (doxazosin) appears to be the least effective of the four in preventing heart failure. Although heart failure was not the main focus of the study, the study reviewers have decided that the difference is important enough to notify me, and for me to notify you.

It is very important that we meet together to decide on a treatment for your high blood pressure, discuss what the study results mean for you, and answer questions that you have. Please call my clinic by the end of March at the number listed below to make an appointment. DO NOT STOP TAKING YOUR ALLHAT MEDICINE UNTIL WE DECIDE ON THE BEST TREATMENT FOR YOU, BECAUSE THE MEDICINE IS HELPING TO KEEP YOUR BLOOD PRESSURE CONTROLLED. Be sure to bring your ALLHAT medicine to the clinic with you. At that time, a different medicine also being used in ALLHAT will be available to you free of charge. Blood tests required by the study will still be free.

You are also a valuable participant in the cholesterol-lowering part of ALLHAT. You were assigned to receive the cholesterol-lowering medicine Pravastatin, and it will still be provided to you free of charge. Since that part of the study will continue, you should continue with your ALLHAT visits every four months and try to follow the dietary recommendations given to you.

All of us who are conducting ALLHAT greatly appreciate your participation, which has helped us to answer one question. We depend on your continued participation to help us find the benefits of lowering serum cholesterol in people whose serum cholesterol is slightly elevated.

Sincerely,

Address
Phone

Center and site #

ALLHAT

Important Questions & Answers about ALLHAT!

1) Q. Why is ALLHAT discontinuing the drug doxazosin?

A. As you may recall, one of ALLHAT's goals is to learn which of four types of high blood pressure medicines are the best in helping to control blood pressure and lowering risk of heart disease, stroke and early death. Because of your participation in ALLHAT, we have learned that doxazosin, one of the study medicines, is not working to lower the risk of some heart diseases as well as other blood pressure medicines can. This is exciting to ALLHAT because we have answered one of the study questions earlier than expected. It also means that ALLHAT no longer needs to study the medicine doxazosin.

2) Q. Is doxazosin harmful to my health if I have been taking it?

A. Doxazosin is a Food and Drug Administration (FDA) approved medicine and is used for other types of health problems such as prostate troubles. ALLHAT has not found that Doxazosin is harmful, but the study has found that other high blood pressure medicines may lower your risk of heart disease better than doxazosin.

3) Q. Are the other medicines in ALLHAT safe?

A. Yes, all of the ALLHAT drugs are FDA approved and have been used to lower blood pressure for many years. ALLHAT is learning, through your participation, which of four *commonly used* high blood pressure medicines are best for lowering the risk of heart disease, stroke and early death in patients with high blood pressure. A panel of expert doctors, known to ALLHAT as the Data and Safety Monitoring Board, watches the information gathered from your ALLHAT visits and advises the National Heart, Lung and Blood Institute. Their job is to make sure that you are safe while participating in ALLHAT. If they detect that the medicines in the study are not helpful or are harmful to you then steps will be taken to make sure you stay safe.

4) Q. If I am assigned to the drug doxazosin, what should I do?

A. If you have been informed through a letter from your ALLHAT clinic that you are **currently taking the medicine doxazosin it is important** that you:

1) **KEEP TAKING** your ALLHAT medicine doxazosin, as it is helping to keep your blood pressure controlled, until you can meet with your doctor to decide if a different high blood pressure medicine is right for you;
2) Call your ALLHAT clinic and make an appointment to meet with your doctor within one month of receiving the letter;
3) Bring your ALLHAT medicine to your ALLHAT appointment;
4) Understand that this will be your last ALLHAT visit ***unless*** you are participating in the lipid-lowering part of the study;
5) Remember that your participation in the ALLHAT has helped researchers to answer a very important question about high blood pressure medicine and you have been a valuable participant; and
6) **Support your family and friends** who will be continuing with ALLHAT to take their medicines and keep their ALLHAT visits!

5) *Q. If I have been assigned to doxazosin and I am also in the lipid -lowering part of the study, will I still continue to be involved with ALLHAT?*

A. YES! You are a valuable participant in the in the lipid-lowering part of ALLHAT. You will continue to visit your ALLHAT doctor every four months. **You will also continue to be given medication to control your blood pressure.** Please be sure to:

1) **KEEP TAKING** the medicines given to you by your ALLHAT doctor;
2) Keep following any dietary advice that your doctor gives you;
3) Make an appointment in the next month to discuss your high blood pressure medicine with your doctor if you are currently taking doxazosin; and
4) KEEP coming to your ALLHAT visits!

6) *Q. If I am NOT assigned to the medicine doxazosin, why is it important that I continue to participate in ALLHAT?*

A. If you were NOT assigned to take doxazosin then it is ***very important for you to continue*** your participation in ALLHAT because we are still learning which medicines are the BEST at lowering health risks connected with high blood pressure. Your participation is the only way that we can answer this question! Please remember to:

1) **KEEP TAKING** your high blood pressure medicine, as it is helping to keep your blood pressure controlled;
2) Attend your regularly scheduled ALLHAT visits every four months; and
3) Continue to support other family and friends who are also a part of ALLHAT!

ALLHAT

7) *Q. If I have not been keeping up with my scheduled ALLHAT visits or have lost touch with my ALLHAT clinic, how can I get re-involved?*

A. If you are an ALLHAT participant but have not been taking your ALLHAT medicine, have missed appointments or have moved and do not have a new ALLHAT clinic we would like to hear how you are doing! You are still a part of ALLHAT and a very important part of the study. **Please call your last ALLHAT clinic.** We would like the opportunity to speak with you and answer any questions you may have.

8) *Q. If I am no longer in ALLHAT, how will my blood pressure be treated now?*

A. If you are one of the participants assigned to doxazosin and will no longer be participating in ALLHAT then your blood pressure health will now be treated by your regular family doctor. During your final ALLHAT visit your ALLHAT doctor will:

- Give you enough blood pressure medicine to last through your change from ALLHAT to regular care;
- Answer any questions you may have about high blood pressure and the future of your care.

If your family doctor is not your ALLHAT doctor then your ALLHAT doctor will also:

- Notify your family doctor of the changes happening with ALLHAT; and
- Help you find a family doctor if you do not already have one.

Q. I have questions about the changes in ALLHAT and how it affects me, whom should I ask?

A. We understand that you may have additional questions about the changes in ALLHAT and your future as a participant. Please ***write your questions down*** and bring them with you to your **next** ALLHAT visit. Your doctor will be able to go over your questions and help you to find the answers.

More ALLHAT Questions and Answers

Revised 3/1/00

1. ***What is the reason for the higher rate of CHF in doxazosin users?***

   One explanation for the superiority of chlorthalidone is that this drug is very effective in preventing CHF. Doxazosin may have no effect ("a placebo-like effect") in CHF prevention. If doxazosin precipitates CHF, which cannot be concluded in ALLHAT, several possible mechanisms may be hypothesized and deserve further investigation.

2. ***How much of the difference in cardiovascular event rates between chlorthalidone and doxazosin can be explained by the observed 2-3 mm Hg difference in SBP?***

   At least some of the difference in the risk of CHF and much of the difference in the risk of stroke may be explained.

3. ***Is doxazosin harmful in patients with hypertension?***

   ALLHAT compared 3 active drug regimens against an active standard regimen. Since there was no placebo or "no treatment" arm, it was not designed to evaluate the potential for any of the drug treatment arms causing harm. A comparative trial like ALLHAT can only determine whether a new treatment is superior, equal or inferior to a standard treatment. ALLHAT has shown that doxazosin is inferior to the diuretic chlorthalidone as initial treatment.

4. ***Is doxazosin harmful if used in normotensive patients with BPH?***

   ALLHAT did not study normotensive patients and, thus, cannot answer that question. Whether doxazosin causes CHF in normotensive patients with BPH deserves investigation.

5. ***Do the findings for doxazosin extend to other alpha-blockers?***

   They might very well do so, but no firm conclusions can be drawn. The question needs an answer. Until the answer is available, alpha-blockers should not be considered first-line (initial) therapy to lower elevated blood pressure in older hypertensive patients.

6. ***ALLHAT is also investigating two other drugs, a calcium antagonist and an ACE inhibitor. Are these drugs also inferior to chlorthalidone?***

   After accumulating over half of the information expected, ALLHAT has not yet reached any conclusions for these drugs. ALLHAT continues with ongoing oversight by a Data and Safety Monitoring Board, and the answer will be available in 2 years or earlier.

7. ***Since ALLHAT continues the amlodipine treatment, can one conclude that calcium antagonists are safe?***

   After accumulating over half of the information expected, ALLHAT has not yet reached any conclusions for these drugs. ALLHAT continues with ongoing oversight by a Data and Safety Monitoring Board, and the answer will be available in 2 years or earlier.

8. ***My father is on doxazosin. Should he stop taking this drug immediately?***

No, he should continue taking his medication at least until he has seen his physician. We know that doxazosin is beneficial in lowering elevated cholesterol levels and for BPH. After reviewing your father's individual circumstances, the doctor may or may not think that another treatment will be of more benefit.

9. ***Do the ALLHAT results apply to the use of doxazosin in combination with other antihypertensives?***

Doxazosin was used as initial therapy in ALLHAT. Whether it has value as "add on" therapy to achieve blood pressure control was not examined.

10. ***Could the increased CHF noted in ALLHAT simply be the result of the overdiagnosis of CHF in patients who develop edema/fluid retention from doxazosin?***

That possibility was considered, but after detailed evaluation of clinical information on a sample of the cases, we believe it was not an important factor, and in particular could not explain the significantly higher combined rate of hospitalized and fatal CHF in the doxazosin arm.

11. ***Why was this part of the trial not stopped earlier?***

Several considerations were deliberated by the Data Safety Monitoring Board, the Project Office, and the Clinical Trials Center when the difference in a major secondary endpoint between the doxazosin arm and the chlorthalidone arm appeared to be significant and in favor of the chlorthalidone. First it was noted there was no difference in the primary endpoint or in total mortality; second, it was noted that the major portion of the endpoint which was different was CHF events and further evaluation was needed to be assured that the cases reported were real and of similar severity in the two arms; and third, the average cholesterol level was lower (as expected) in the doxazosin arm and there was consideration of the potential of delayed benefit that might counterbalance the reduced prevention of CHF disadvantage. The next review was done in six months rather than the usual 9-12 months. At that time the overall evidence was more convincing that a protocol change should be made; the overall trends persisted and the statistical evaluation showed that the likelihood of doxazosin proving superior to chlorthalidone by the end of ALLHAT was extremely unlikely.

12. ***Why did NHLBI ask an independent review group as well as the DSMB to review the ALLHAT data?***

The decision as to whether a change in the ALLHAT protocol of the magnitude of stopping one arm must be finally made by the Director of NHLBI, with advice from the DSMB and others, including independent experts, if necessary. Because the DSMB vote on the issue of whether to continue the doxazosin arm was a split vote with several members on each side of the issue, the Director, NHLBI, chose to obtain additional advice from independent experts as well. They unanimously recommended stopping the arm. Though it has not occurred very often in the past, NHLBI directors have sought advice from independent experts in similar difficult situations in large clinical studies.

Major Cardiovascular Events in Hypertensive Patients Randomized to Doxazosin vs Chlorthalidone: Preliminary results from ALLHAT

Dr. Barry Davis

The first outcome results from the Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial (ALLHAT) are presented here. This [presentation] is on behalf of the ALLHAT research group, a very large group. The title is Major Cardiovascular Events in Hypertensive Patients Randomized to Doxazosin vs Chlorthalidone. There were 16 members in the steering committee. ALLHAT has 625 clinical sites located in the United States, Canada, Puerto Rico, and the US Virgin Islands. The sites consist of VA Hospitals, private medicine hospitals, and community health centers, HMO and specialty practices.

Methodology

ALLHAT is a practice based, randomized, multi-center trial with two components; an antihypertensive component and the other a lipid-lowering component. [What was presented at the ACC] was restricted to the hypertensive component.

[In this trial] 42,448 high risk hypertensive patients, ≥ 55 years of age were randomly allocated to one of four treatment groups. **The primary objective was [to determine] whether new hypertensive agents reduced the incidence of primary heart disease compared to a diuretic.** The trial was blinded and no placebos were used. The treatments used were the diuretic chlorthalidone, the calcium channel-blocker amlopidine, an alpha-blocker doxazosin, and an ACE-inhibitor lisinopril. The scheduled follow-up for the study was 4 to 8 years, with an average of 6 years.

Secondary outcome [measurements] of the trial included:

- All cause mortality
- Stroke
- Combined CHD which included non-fatal MI, CHD death, coronary revascularization, hospitalized angina
- Combined CVD, which included combined CHD, stroke, lower extremity revascularization, treated angina, fatal/hospitalized/treated CHF, or hospitalized or outpatient PAD.

Inclusion criteria for the trial included either men or women, aged 55 years or older, with a history of hypertension (having been previously documented or on treatment, or they could be newly diagnosed prior

or at the first two visits of ALLHAT according to JNC V criteria). Patients also had to have at least one of the following:

- MI or stroke (age-indeterminate or at least 6 months old)
- History of a revascularization procedure
- Other documented ASCVD
- Major ST segment depression or T-wave inversion
- Type 2 diabetes
- HDL-C < 35 mg/dL on two occasions
- Left ventricular hypertrophy by ECG or echo in the last two years
- Current cigarette smoker

Results

15,268 people were randomized to the chlorthalidone arm and 9,067 were randomized to doxazosin arm. At baseline mean systolic/diastolic blood pressure was 146/84 mm Hg,, mean age in the trial was 67 years, 33% were African-American, 46% were women, 22% were current cigarette smokers, and 46 % had a history of atherosclerotic cardiovascular disease, and 35% had Type 2 diabetes.

The results for medication adherence [show that] at 4 years, 86% of the patients that were assigned to chlorthalidone were still on chlorthalidone or still taking a diuretic, while 75% of those assigned to doxazosin were still on doxazosin or another alpha-blocker.

The [systolic] blood pressure results indicate that at baseline the common blood pressure was 146 mm Hg, [however, by the fourth year] the doxazosin group had a mean blood pressure of 137 mm Hg and the chlorthalidone had [a mean systolic blood pressure of] 135 mm Hg. The diastolic blood pressure results [indicate] that at baseline and throughout they [remained] the same. At baseline [the diastolic blood pressure] was 84 mm Hg and by [the fourth year] it was 76 mm Hg in both groups.

On January 24th of this year, the director of the NHLBI accepted the recommendation of an independent review committee to terminate the doxazosin arm of the study. This [decision] was based on two reasons:

- **One was the futility of finding a significant difference for primary outcome of CHD by the scheduled end of the trial.**
- **The second [reason] was that there was a statistically significant 25% higher rate of a major secondary outcome of combined cardiovascular disease [in the doxazosin arm].**

Dr. Curt Furberg [presented the remaining material on clinical outcomes]

The principal reason for stopping the doxazosin arm was the 25% difference in the secondary outcome combined cardiovascular disease.

[In ALLHAT] there were more than 15,000 patients randomized to the chlorthalidone group, 9,000 to the doxazosin group. At four years of follow-up, 2000 patients [were] in the chlorthalidone group and 1,000 in the doxazosin group [both were followed up through the 4 year point]. If you look at the cumulative event curves [of the doxazosin group vs the chlorthalidone group] they diverge [after] the first year. **The 4-year event rate in the doxazosin group was 26%. The relative risk [of CHD] for the entire study 1.25. [There was] a 25% difference [between the two treatment arms] with very narrow confidence intervals. The z-score was 6.77 which corresponds to the P value of <0.0001.**

The main contributor to this difference in combined cardiovascular events was congestive heart failure. The [cumulative event rate] curves diverge from early in the first year with a much higher rate in the doxazosin group. The event rate in the chlorthalidone group was about 1% per year and twice that in the doxazosin group. [The cumulative event rates for CHF had a] relative risk of 2.04, the confidence intervals were very tight and the Z-score was almost 11 and the [corresponding] P-value had 26 zeros. To illustrate the strength of the finding these data are based on a total of 900 patients developing heart failure during the study. The approximately two fold [increase] in rate of CHF was seen consistently in all major sub-groups treated with doxazosin. The same [results were found] for men and women in different groups based on ethnic backgrounds [ie, white non-Hispanic, Hispanic, and black]. A very similar finding [was discovered] for the patients enrolled with or without diabetes.

If the heart failure events are subtracted from the cardiovascular events there still is a statistically significant difference in the cumulative event rate. This difference is small; it is about 13%. [However, because of the size of the study the [corresponding] P-value is < .001. **The major contributor to this difference in non-CHF cardiovascular events [between the two treatment arms] was stroke.** The survival event curves [show a slightly different] pattern and the curves continue to diverge over 4 years of observation. **The event rate of the chlorthalidone group was 0.9% and it was about 20% higher in the doxazosin group. The relative risk (RR) is 0.19 and the nominal p-value was .04.**

The primary outcome defined by the protocol was the combined rate of CHD mortality and non-fatal MI and there was no difference [between the two outcomes]. **The 4-year [event] rates were in excess of 6% and the RR was 1.03.** When the decision to terminate the doxazosin arm was made, about 61% of the

expected primary events in the chlorthalidone group [had occurred]. **Conditional power calculations of the likelihood of doxazosin showing a benefit for primary outcome at the end of the trial was < 1%.** Thus futility became another reason for discontinuing the doxazosin arm. The other arms of the trial [will] continue.

Based on our findings, the overall conclusion is that chlorthalidone is clearly superior to doxazosin for three reasons:

- **Hypertension control – [there was] a lower mean systolic blood pressure in the chlorthalidone group and there were fewer patients requiring step up medications in the diuretic group [compared to the doxazosin group].**
- **Chlorthalidone was also superior [to doxazosin] in drug compliance; more patients in the doxazosin group dropped out because of adverse events.**
- **There was a fairly significant reduction in cardiovascular complications [found early on in the trial] in the chlorthalidone group.**
- **In addition, chlorthalidone is ten times less expensive than doxazosin.**

[The results from ALLHAT] have taught us several lessons.

- In some drugs blood pressure lowering is an inadequate marker or surrogate of health benefits in hypertension.
- Anti-hypertensive drugs can have important non-blood pressure actions that may alter the blood pressure lowering.
- Comparative outcome trials, like ALLHAT, are essential for documenting optimal drug benefits/risk balance and for guiding clinical practice. ALLHAT has shown that major relevant events of interest should be evaluated.

In summary, our recommendations are straight forward; chlorthalidone (or probably any diuretic) remains the recommended drug of choice for antihypertensive treatment. Doxazosin is not recommended as first line therapy. These findings [discussed here] likely apply to all alpha-blockers. Until proven otherwise it seems prudent to at least assume that doxazosin is also inferior as a second or third line hypertensive agent and the long term cardiovascular safety of alpha-blockers and BPH should be investigated.

FOR IMMEDIATE RELEASE
March 23, 2000
Contact:Beth Cassady or Melanie Caudron
301-897-2628
media@acc.org

ACC Clarifies Clinical Alert on Alpha Blockers for Hypertension Treatment

(BETHESDA, MD)-The American College of Cardiology (ACC) is clarifying its previously released information on alpha-adrenergic blockers for the treatment of hypertension to emphasize the intent of its March 15, 2000, statement. The ACC Clinical Alert on Alpha Blockers for Hypertension stated that physicians should carefully reassess the use of alpha blocker doxazosin (Cardura®), rather than automatically discontinuing its use, based on the findings of a study sponsored by the National Heart, Lung, and Blood Institute (NHLBI). The ACC strongly encourages physicians to review the NHLBI data and statement for clarity and guidance in treating hypertensive patients.

The ACC clinical alert followed announcement of the results of a large study on the treatment of hypertension on March 15 at the ACC 49th Annual Scientific Session in Anaheim, Calif.

In its official statement, which follows, the ACC Hypertensive Diseases Committee urged patients taking an alpha blocker to see their physicians for reassessment. "This is important because the treatment of hypertension and the choice of medication should be individualized for each patient," stated Committee Chair Dr. Robert J. Cody.

The ACC clinical alert can also be found at www.acc.org.

ACC Clinical Alert on Alpha Blockers for Hypertension (released March 15, 2000)
The American College of Cardiology (ACC) recommends that physicians reassess use of a widely prescribed drug, an alpha-adrenergic blocker, for the treatment of hypertension. This recommendation follows announcement of the results of a large high blood pressure study on March 15, 2000, at the ACC 49th Annual Scientific Session in Anaheim, Calif. Approximately 50 million Americans have hypertension, or high blood pressure.

The study was halted last week by the study sponsor, the National Heart, Lung, and Blood Institute (NHLBI), due to data showing that the alpha blocker, doxazosin (Cardura®), is less effective than the more traditional diuretic in reducing some forms of cardiovascular disease, such as congestive heart failure. The study, Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), showed that users of doxazosin had 25 percent more cardiovascular events and were twice as likely to be hospitalized for heart failure than users of the diuretic chlorthalidone.

According to the NHLBI, of the 24 million Americans who take medication to treat their hypertension, about one million use an alpha blocker. "The ACC encourages physicians who treat hypertensive patients to review the new data with their colleagues to ensure the

rapid dissemination of this important information," said Dr. Robert J. Cody, chair of the ACC Hypertensive Diseases Committee and associate chief of the Cardiovascular Division at the University of Michigan Medical School in Ann Arbor. "At the same time, hypertensive patients taking an alpha blocker should first see their physicians before discontinuing its use. This is important because the treatment of hypertension and the choice of medication should be individualized for each patient."

The results were presented at the ACC meeting by Dr. Curt Furberg, of the Wake Forest University School of Medicine in Winston-Salem, N.C., and Dr. Barry Davis, of the University of Texas School of Public Health in Houston. For more information about the ALLHAT study, go to www.nhlbi.nih.gov and go to "news" and "press releases."

The American College of Cardiology, a 25,000-member nonprofit professional medical society and teaching institution, is dedicated to fostering optimal cardiovascular care and disease prevention through professional education, promotion of research, leadership in the development of standards and guidelines, and the formulation of health care policy.

FAX TRANSMITTAL

TO:	**Dr. Jeff Cutler** **Dr. Barry Davis** **Dr. Jackson Wright**	**FAX: (301) 480-1773** **(713) 500-9530** **(216) 368-4752**
FROM:	**Dr. Curt D. Furberg**	**FAX: (336) 716-0395**
DATE:	**March 8, 2000**	

TOTAL PAGES: 3

If there are any problems receiving this message, please call (336) 716-2498.

Attached please find a copy of Pfizer's statement on Cardura and ALLHAT.

Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755

PFIZER STATEMENT ON CARDURA AND ALLHAT

New York, March 8 — Pfizer supports the National Heart, Lung, and Blood Institute's (NHLBI) decision to discontinue the Cardura arm of the ALLHAT trial. Pfizer is a major supporter of ALLHAT and is working with the NHLBI while these findings continue to be analyzed.

In the ALLHAT trial, Cardura was compared to a diuretic (chlorthalidone). With the long-term trial not expected to conclude until 2002, the Cardura arm was discontinued because Cardura is not expected to show superior efficacy based on current data. Cardura and the diuretic had similar results in reducing heart attack and death. However, Cardura was significantly less effective in preventing the development of congestive heart failure than the diuretic, an agent proven to reduce the risk of developing CHF as well as an approved treatment for CHF

In the clinical practice of managing hypertension, Cardura is predominantly prescribed and used in combination with other antihypertensive medicines. In contrast, in the ALLHAT trial Cardura was used as initial therapy. For the treatment of BPH, Cardura is generally used as a first-line agent.

In general, hypertension treatment guidelines recommend Cardura as a combination agent for patients not adequately controlled on one (or more) antihypertensives. Treatment guidelines also recommend Cardura for the management of hypertension accompanied by conditions such as BPH.

Cardura remains a safe and effective treatment for hypertension and BPH when used appropriately.

Since its introduction in 1988, the wide prescribing experience with Cardura (doxazosin) underscores its efficacy and safety in the management of hypertension and/or benign prostatic hyperplasia (BPH). Cardura is the most extensively studied alpha-blocker ever.

Cardura (doxazosin) has been used in over 45 countries for hypertension and/or benign prostatic hyperplasia since 1988. There have been more than 3.4 billion patient days of Cardura therapy worldwide.

Contacts: Maryann Caprino
212-733-5686
Vanessa McGowan
212-733-3784

Flapan, Valerie
From: Barry, Ann
Sent: Sunday, February 13, 2000 1:45 PM
To: Flapan, Valerie; Holmes, Patrick; Sainpy, Marie-Caroline
Subject: FW: Cardura in ALLHAT

—Original Message—
From: Feczko, Joe
Sent: Sunday, February 13, 2000 1:33 PM
To: Barry, Ann; Sweeney, Mike; Helgans, David; Widlitz, Michael; Brinkley, David; Natalicchio, Teri; Walmsley, Patricia A
Subject: RE: Cardura in ALLHAT

Ann
This is a very clear discussion of the meeting we had with the NIH and the interpretation of the study. I agree we need to understand this area better.
We cannot and should not try to change the mind of the ALLHAT steering com.

Joe

—Original Message—
From: Barry, Ann
Sent: Friday, February 11, 2000 1:38 PM
To: Sweeney, Mike; Helgans, David; Widlitz, Michael; Feczko, Joe; Brinkley, David; Natalicchio, Teri; Walmsley, Patricia A
Subject: FW: Cardura in ALLHAT
Importance: High

I feel compelled to be the devils advocate and comment on Mike's message/suggestions.

First of all, the NIH has made its decision to terminate the Cardura arm of ALLHAT. The decision was carefully and deliberately made, was based on the data, and I believe is irreversible. The NIH convened a committee of heart failure experts that reviewed the data and recommended the Cardura study arm be stopped to ensure the safety and efficacious treatment of study participants. If Pfizer challenged the decision, it would appear that Pfizer was more concerned about product image and profits that they are about the welfare of patients. It is also doubtful that continuation of the arm would change the eventual outcome of the study. I do believe that Pfizer needs to strive to understand the mechanisms and the why of the results. This could potentially clarify how Cardura could be safely and effectively used in this population. In the mean time, however, we have no real choice but to accept the stop decision and to do so graciously.

With regard to specific points:

1. I think that the argument that this is not a fair comparison appears defensive and more importantly is probably irrelevant. The argument could have merit if the NIH chose to study Cardura vs the other agents in a heart failure population i.e. used the agents for the "treatment" of heart failure. and then extrapolated the results to a non- heart failure population. ALLHAT, however, randomized elderly hypertensive patients without overt or apparent heart failure. (A patient population where Cardura is frequently used.) The goal of the trial was to determine which agent(s) were most efficacious in reducing cardiovascular events - events that include development of heart failure as well as MIs etc. The data show that in this hypertensive population (a population where Cardura and chlorthalidone are

frequently used) Cardura was less effective overall in reducing cardiovascular events than was chlorthalidone. That IS the bottom line. We cannot argue that or change that.

While there is certainly no harm in looking at the heart failure risk in Framingham, it will provide no definitive answers or ammunition. Framingham is a different population that will have a different level of risk.

2. The difference in stroke rates between Cardura and chlorthalidone can probably be explained almost entirely by the difference in SBP. It does appear, however, that BP cannot explain all of the difference in the heart failure events. The question then becomes, is chlorthalidone doing something else positive or is Cardura doing something negative. We do not know the answer to this question. I believe that Pfizer must try to determine if there are any potential operative mechanisms that could explain the difference. We must honestly try to determine if Cardura does have a negative effect in some patients. The ALLHAT DSMB and Steering Committee are evaluating and making decisions based on clinical results. For the most part, they are not the best individuals to elucidate mechanisms. I believe Pfizer needs to initiate discussion with some heart failure experts such as Milton Packer who could help us determine some potential mechanisms and help us determine how to address them.

For example, a plausible suggested mechanism could be related to levels of DBP. In pushing the dose and adding agents in an attempt to lower SBP, it is possible that with Cardura DPBs are at some points in time too low to provide adequate coronary perfusion. This in turn would compromise LV function. Since DBPs could be fluctuating over time, this might not be readily picked up by the infrequent cuff measurements. If people like Milton believed that inadequate coronary perfusion were a real possibility, despite the limitations it could still be worthwhile seeing if the NIH could look at DBPs of the patients with heart failure events vs. those with no HF events. It may be that Cardura would be fine in patients where DBPs are at a reasonable level and coronary perfusion is maintained.

I don't see a benefit to dwelling on the "just unmasking of preexisting LV dysfunction" as though it could discount the results. First, the NIH feels it is probably not the case. They did an analysis eliminating the first year data and starting with year 2 as a baseline. The same diverging effect was apparent. Secondly, even if it were the case,it stills means that elderly patients in the real world who often have some degree of undiagnosed LVD would be better treated with chlorthalidone than with Cardura.

3. The cancer event rate for Cardura in ALLHAT is numerically less than with chlorthaidone with a relative risk of 0.9. There is, however, no statistical difference (p=0.16) and the Steering Committee believes the numerical difference has little meaning. The DSMB believes that the lack of any pattern in the type of reported cancers further supports no causality. To say that Cardura decreases cancer because it increases prostatic apoptosis requires a huge leap of faith and I am not sure it is in our best interest to go down that road. Even if the differences were real, it does not offset the significant difference in cardiovascular events.

4. Postulating beneficial effects based on positive attributes is valuable and has merit particularly when no long-term event data is available. However, you are always postulating because no one can ever know all of the operative mechanisms or their relative importance. Using the Framingham risk equation definitely has value in some settings. However, one has to question how far that will go in terms of dealing with hard numbers, hard end-points and events that are staring us all in the face..

I believe we do need to try to elucidate potential mechanisms, we need to show that we honestly care about the clinical effects of our agents in patients. However, we do not want to be viewed as trying to explain away results and discounting actual clinical events.

Ann

—Original Message—
From: Feczko, Joe
Sent: Tuesday, February 08, 2000 1:05 PM
To: Walmsley, Patricia A; Barry, Ann
Subject: FW: Cardura in ALLHAT
Importance: High

—Original Message—
From: Sweeney, Mike
Sent: Friday, February 04, 2000 8:57 AM
To: Helgans, David
Cc: Natalicchio, Teri; Widlitz, Michael; Feczko, Joe; Brinkley, David
Subject: Cardura in ALLHAT
Importance: High

David,

Following your briefing of me yesterday evening on the issues surrounding the inclusion of Cardura in the ALLHAT study I have had a chance to think further on this overnight and would like to summarise my suggestions (including those which we discussed yesterday).

1. I agree with you that it is not a fair comparsion to compare the incidence of CHF with Cardura to the incidence of CHF using treatments known to be beneficail in this condition (i.e. diuretics, Norvasc and ACEi). I would suggest that a more reasonable comparison would be to the expected incidence of CHF based on the Framingham risk factor profile of the patients at entry. This should show that less cases than were predicted to occur did. I agree with you that a comparison of combination therapy with monotherapy is warrented to further explore this effect.

2. CHF secondary to hypertension is very unusual these days. It almost always follows ischemia or cardiomyopathy. I would ask the steering committee for a hypothesis to explain the apparent increase in CHF if the incidence of ischemia is identical. Without precipitation by ischemia this effect is probably just the unmasking of preexisting LV dysfunction which the effective therapy for CHF which the other agents deliver is preventing. The VeHFT 1 study show that alpha blockade has no effect on the progression of CHF.

3. I understand that the overall mortality/morbibity for Cardura is neutral due to a large difference in the incidence of cancer with Cardura compared to diuretics. I would argue that this is due to a direct effect of Cardura. Kypriano et al published about 2-3 years ago that Cardura increases the rate of apoptosis (programmed cell death) in prostate tissue. An increased rate of apoptosis would be expected to lead to a reduction in the incidence of malignancy. To remove Cardura form the study now would potentially deny such a benefit to patients currently on this treatment. I am not totally au fait with this work so it would be worth while looking into the literature in this regard. Dr Georg Bartsch of Innsbruck, Austria, commenced some further work addressing this hypothesis following Dr Kypriano's work and he may be the best person to advise.

4. You mentioned that the lipid levels had trended in the correct direction during the study. These changes should be input into the Framingham equation to predict a 10-20 year change in CAD which would result. In addition the changes should be compared with those in the 4S and WOSCOP's studies to see if such changes would have resulted in a reduction in endpoints in only 4 years.

Whilst these arguements may not be enough to persuade the steering committee to retain Cardura they at least allow us to argue from a scientific perspective that such an exclusion is not mandated based on the data to date.

I hope this is helpful,

Mike

Flapan, Valerie

From: Henderson, John
Sent: Monday, April 03, 2000 5:29 PM
To: McLaughlin, Peggy
Cc: Mallen, Sharon; Picciano, John X; Wittich, Rita; Logalbo, Suzanne; Gribko, Greg; Dieck, Gretchen; Walmsley, Patricia A; Helgans, David; Widlitz, Michael; Oleksey, Karole M.; Petchel, Kasia; Flapan, Valerie; Phyfferoen, Monique; Raillard, Pierre; Moutzouris, Nick
Subject: RE: URGENT: ALLHAT Medical Summary

Peggy,
I presume that the report contains only information that is already in the public domain; is this correct? Do we know if the differences in combined CHD and in stroke are statistically significant? The combined CVD is statistically significant but we do not offer this information. Is this because we do not have sufficient information to understand how the analysis was done? If we do know how the analysis was done, should we not offer this information?
There is no reference to when CHF was diagnosed but I understand that this was early relative to randomisation. This is surprising and raises several questions; is this not a point to be made?
You say the groups were similar at baseline; were there any statistical differences?
In the description of the Pfizer position, have you considered the patterns of use of doxazosin outside the USA? In some countries I understand that we are labeled to allow first line therapy. We need to make sure the message is appropriate for all countries.
I would have thought that one conclusion that we might draw is the importance of effective control of high blood pressure. If the difference between the two treatments is a reflection of a 3mm difference in systolic, then the message is loud and clear - effective control is critical.
Best wishes,
john

—Original Message—
From: Mallen, Sharon
Sent: Friday, March 31, 2000 6:28 PM
To: Picciano, John X; Wittich, Rita; Logalbo, Suzanne; Gribko, Greg; Dieck, Gretchen; McLaughlin, Peggy; Walmsley, Patricia A; Helgans, David; Widlitz, Michael; Oleksey, Karole M.; Henderson, John; Petchel, Kasia; Flapan, Valerie
Subject: URGENT: ALLHAT Medical Summary
Importance: High

Dear all,

Attached is a DRAFT Medical Summary addressing Pfizer's position on ALLHAT. Please review and provide comments to Peggy McLaughlin ASAP, but no later than close of business on Monday, April 3, 2000.

Thanks,
Sharon

<< File: ALLHAT medical summary.doc >>

FROM: Otano, Andres
TO: Gavigan, Michael; Silber, Beth Ann
CC: Wickwire, Michele M; Hayes, Philip J; Reggio, Dick; Barry, Ann
SUBJECT: FW: ALLHAT RESPONSE
DATE: 20000321

Mike and Beth-
From the Midwest, I will forward more significant responses and successes as I receive from the regions.

Focus on Significance

Andy Otaño
Sales Ops-Specialty
3-2768

-----Original Message-----
From: Hayes, Philip J
Sent: Monday, March 20, 2000 8:06 PM
To: T5DH1, USPFF; T5DH3, USPFF; T5DH4, USPFF; T5A00, USPFF; T5B00, USPFF; T5C00, USPFF; T5D00, USPFF
Cc: Wickwire, Michele M; Putnam, Duane C; Allen, Henry F; Otano, Andres; Reggio, Dick
Subject: ALLHAT RESPONSE

Dear ROUs and CHRs:

It is extremely important that everyone selling Cardura gives a consistent, unambiguous and powerful response to a physician's questions about Cardura and ALLHAT. Based on feedback from a number of sources, the following responses are appropriate.

We should immediately ensure that high-prescribers of Cardura clearly understand the messages outlined below. Targeting high-prescribers using Sherlock and immediately addressing any concerns they might have is imperative. If we do this, we can prevent any misunderstandings.

Potential Responses

UROLOGIST

"Doctor, I understand how strongly you feel about your patient's well being and quality of life. Cardura is an exceptionally safe drug, and the most extensively studied alpha blocker. The NHLBI did not conclude that the drug was harmful. As a matter of fact, Cardura was similarly effective in preventing heart attacks and in reducing the risk of death from all causes. The diuretics seemed to work better at reducing cardiovascular disease: predominantly CHF, and to a lesser degree, stroke. They of course, provide your patients with no positive effects on their urinary symptoms. If your goal is to provide your patients with safe and effective relief from the irritating and troublesome effects of BPH, you can find no better choice than Cardura."

Primary Care

"Doctor, I understand how strongly you feel about your patient's well being and quality of life. Cardura is an exceptionally safe drug, and the most extensively studied alpha-blocker. The NHLBI did not conclude that the drug was harmful. As a matter of fact, Cardura was similarly effective in preventing heart attacks and in reducing the risk of death from all causes. The diuretics seemed to work better at reducing cardiovascular disease: predominantly CHF, and to a lesser degree, stroke. Cardura provides an aging hypertensive male not only with additional control of his blood pressure, but relief from his debilitating urinary symptoms. It would be torture to give a middle-aged man with BPH a diuretic. He certainly doesn't need the increased urgency. Cardura gives relief, improves his quality of life, and helps control his hypertension while doing no harm."

Cardiologist

"Doctor, I understand how strongly you feel about your patient's well being and quality of life. Cardura is an exceptionally safe drug, and the most extensively studied alpha-blocker. The NHLBI, as you know, did not conclude that the drug was harmful. As a matter of fact, Cardura was similarly effective in preventing heart attacks and in reducing the risk of death from all causes. The diuretics seemed to work better at reducing cardiovascular disease: predominantly CHF, and to a lesser degree, stroke. Cardura provides a tremendous value to you and your patients through its unique ability to provide the aging hypertensive male with a tremendous weapon in his almost inevitable battle with BPH, while at the same time giving you a safe choice to add to other cardiovascular drugs."

A Great Response, regardless of physician specialty:

"Doctor, Cardura is as effective as diuretics in reducing heart attacks and overall deaths. The only difference in the ALLHAT trials was a higher rate of heart failure. When you think about that, Doctor, diuretics are indicated for

the treatment of heart failure. So it doesn't surprise me that there would be less heart failure in the diuretic group."

Remember the basics

1. Listen: Be vigilant for this objection.

2. Clarify: Is the physician concerned about starting new patients?
Has she had patients call to be taken off Cardura?
Is she talking about hypertensive patients or patients with BPH?

"Doctor, what are your concerns?"

3. Empathize: "Doctor, I can understand your concern for your patients overall health."

4. Show Proof: Excerpts from the NHLBI press release explain why the physician can confidently continue prescribing Cardura to his hypertensive and BPH patients:

* "The drugs were similarly effective in preventing heart attacks and in reducing the risk of death from all causes."

* "We cannot conclude that the drug was harmful. Rather it didn't work as well as the diuretic in reducing cardiovascular disease (predominantly CHF, and to a lesser degree, stroke)."

* "Those in the doxazosin group had slightly higher systolic blood pressures…. High blood pressure is the chief risk factor for both congestive heart failure and stroke."

The ALLHAT investigator letter provides further proof of Cardura's safety:

* "The primary CHD outcome, and total mortality were not different between the doxazosin and chlorthalidone arms."

* "ALLHAT has not found that doxazosin in harmful, but the study has found that other high blood pressure medicines may lower your risk of heart disease better than doxazosin."

5. Verify: "Doctor, does this answer your question concerning the safety and effectiveness of Cardura in your patients with hypertension and/or BPH?

6. Close: "Doctor, based on the safety and unparalleled power of relief that Cardura provides, will you continue to use it for your middle-aged hypertensive men?"

P.J. Hayes
Specialty Midwest, Side One ARM

FROM: Oleksey, Karole M.
TO: Gavigan, Michael
SUBJECT: FW: PPG ANNOUNCEMENT - EUROPE - ORGANIZATION CHANGES
DATE: 20000322

fyi

-----Original Message-----
From: Oleksey, Karole M.
Sent: Sunday, March 19, 2000 9:44 PM
To: Silbermann, Susan
Cc: Helgans, David
Subject: RE: PPG ANNOUNCEMENT - EUROPE - ORGANIZATION CHANGES

Susan,

It was nice to speak with you on Friday. I promised I would get back to you regarding your questions about ALLHAT.

1) Pfizer Statement?:
The Cardura WWT, working with upper management and Pfizer Corporate Affairs, has decided not to issue a statement on the ALLHAT preliminary results or on the ACC statement. The decision was based on the fact that a Pfizer issued statement in defense of Cardura would likely draw more media attention to the situation. To date, there has been limited media coverage of both the ALLHAT findings and the subsequent ACC statement.
Instead, Pfizer is currently working with both the ACC and the NHLBI on the recent comments which were outside of the scope of the trial (comments on combination use, use in BPH and the discontinuation of all alpha blockers). It is our goal to work with the ACC and NHLBI so that appropriate perspective can be added and statements clarified to physicians.

2) FDA Activities?:
To date, there has been no request by the FDA to review/revise Cardura's label.

3) EU Regulatory Activities?:
We have not heard of any regulatory activities in the EU regarding doxazosin. The only issue which has come up relates to prazosin and its CHF indication in France .

We will continue to keep you apprised of any new developments on these fronts. In the meantime, please do not hesitate to contact us with questions, comments or feedback.

Many thanks.

Best-
Karole

-----Original Message-----
From: Silbermann, Susan
Sent: Sunday, March 19, 2000 7:48 AM
To: Oleksey, Karole M.
Cc: Helgans, David
Subject: R: PPG ANNOUNCEMENT - EUROPE - ORGANIZATION CHANGES

Dear Karole,
Thanks for your note, and in advance, any help that you can give us. As for the visit, let's get the ALLHAT issues under control, and then think ahead a bit more. OK?

Thanks again,
Susan

-----Messaggio originale-----
Da: Oleksey, Karole M.
Inviato: giovedì 16 marzo 2000 2.23
A: Silbermann, Susan
Oggetto: FW: PPG ANNOUNCEMENT - EUROPE - ORGANIZATION CHANGES

Dear Susan,

Congratulations on your new assignment. I wanted to take the opportunity to introduce myself. I joined the Cardura WWT in marketing almost a year ago after spending several years in USPG marketing. I now have responsibility for Italy and Spain (in addition to Asia/AfME) so I am looking forward to working with you.

I saw Loris and Allesssandro here at the ACC this morning at the ALLHAT presentation. I am sure they will fill you in on the presentation of results. The good news is that they were quite brilliant in sending their key physicians to sightsee rather than hear Curt Furberg slam Pfizer once again!

Once we can stabilize the ALLHAT situation over the next few weeks, I would like to schedule some market visits and would be very interested in meeting with you and your team. Please let me know if this would be possible. In the meantime, please let me know if I can be of any immediate assistance in refining your strategies with Cardura (especially in light of ALLHAT).

I look forward to meeting you soon.

Best Regards,

Sent: Wednesday, March 08, 2000 4:35 PM
To: McCrorie, Hank
Cc: Gavigan, Michael; Natalicchio, Teri; Oleksey, Karole M.
Subject: NHLBI ALLHAT Press Release

March 8, 2000

TO: LABS
PRATT
CHRs
URO
NHO
CECs

FROM: Hank McCrorie

As a further follow-up to the ALLHAT documents sent earlier, attached is the NHLBI press release issued today on ALLHAT, as well as Pfizer's response statement (which will be issued to media outlets through Corporate Affairs if contacted). We are finalizing a Press Release Q&A that will be issued shortly. As the NIH has now made the ALLHAT results public, we are now allowed to discuss this issue with physicians when asked.

We hope this information provides more background on ALLHAT.

On behalf of the Cardura Worldwide Team

David Helgans (212) 573-7390
Michael Gavigan (212) 733-6249

BatesLast: 00000263

Att First: 00000261

Att Last: 00000271

SOURCE: CARDURA

PFIZER STATEMENT ON CARDURA AND ALLHAT

New York, March 8 -- Pfizer supports the National Heart, Lung, and Blood Institute's (NHLBI) decision to discontinue the Cardura arm of the ALLHAT trial. Pfizer is a major supporter of ALLHAT and is working with the NHLBI while these findings continue to be analyzed.

In the ALLHAT trial, Cardura was compared to a diuretic (chlorthalidone). With the long-term trial not expected to conclude until 2002, the Cardura arm was discontinued because Cardura is not expected to show superior efficacy based on current data. Cardura and the diuretic had similar results in reducing heart attack and death. However, Cardura was significantly less effective in preventing the development of congestive heart failure than the diuretic, an agent proven to reduce the risk of developing CHF as well as an approved treatment for CHF.

In the clinical practice of managing hypertension, Cardura is predominantly prescribed and used in combination with other antihypertensive medicines. In contrast, in the ALLHAT trial Cardura was used as initial therapy. For the treatment of BPH, Cardura is generally used as a first-line agent.

In general, hypertension treatment guidelines recommend Cardura as a combination agent for patients not adequately controlled on one (or more) antihypertensives. Treatment guidelines also recommend Cardura for the management of hypertension accompanied by conditions such as BPH.

Cardura remains a safe and effective treatment for hypertension and BPH when used appropriately.

Since its introduction in 1988, the wide prescribing experience with Cardura (doxazosin) underscores its efficacy and safety in the management of hypertension and/or benign prostatic hyperplasia (BPH). Cardura is the most extensively studied alpha-blocker ever.

Cardura (doxazosin) has been used in over 45 countries for hypertension and/or benign prostatic hyperplasia since 1988. There have been more than 3.4 billion patient days of Cardura therapy worldwide.

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SOURCE: CARDURA

EMBARGOED UNTIL
Office
March 8, 2000

CONTACT: NHLBI Communications

(301) 496-4236

NHLBI Stops Part Of Study-

High Blood Pressure Drug Performs No Better Than Standard Treatment

The National Heart, Lung, and Blood Institute (NHLBI) has stopped one part of a large high blood pressure study early because one of the tested drugs, an alpha-adrenergic blocker, was found less effective than the more traditional diuretic in reducing some forms of cardiovascular disease.

Called ALLHAT-for Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial-the main portion of the study is comparing newer drug treatments for high blood pressure with a more conventional and less costly treatment. Another portion is comparing treatments for elevated cholesterol.

The NHLBI acted after an independent data review by an advisory committee. Patients were informed as soon as possible thereafter. Those on the alpha-adrenergic blocker were being offered an alternate medication, in consultation with their ALLHAT or personal physician.

The alpha-adrenergic blocker is doxazosin; the diuretic is chlorthalidone. Users of doxazosin had 25 percent more cardiovascular events and were twice as likely to be hospitalized for congestive heart failure as users of chlorthalidone. The drugs were similarly effective in preventing heart attacks and in reducing the risk of death from all causes.

Of the approximately 24 million Americans who take medication to treat their hypertension, about 1 million use an alpha blocker. Doxazosin, the alpha blocker used in ALLHAT, is sold under the brand name CarduraR. (Other alpha blockers used for hypertension are terazosin, sold under the brand name Hytrin, and prazosin, sold under the brand name Minipres).

"This finding adds important information to our understanding of antihypertensive drugs," said NHLBI Director Dr. Claude Lenfant. "No large-scale blood pressure treatment study had ever compared these two classes of drugs. Earlier studies were small and could not, for example, detect an increase in patients' risk of congestive heart failure."

The rest of the ALLHAT study, which began in 1994, will continue as scheduled and is expected to end in 2002.

ALLHAT involves 42,448 patients, enrolled through 623 clinics and centers across the United States, Canada, Puerto Rico, and the US Virgin Islands. About 7,000 U.S. veterans are participating through 69 Department of Veterans

Affairs clinics.

ALLHAT participants are aged 55 or older. Forty-seven percent are women, 47 percent are white, 35 percent are African American, and 16 percent are Hispanic, while 36 percent have diabetes.

On enrollment in the study, participants had been diagnosed with systolic and/or diastolic hypertension (140 mm Hg or higher and 90 mm Hg or higher, respectively), and had at least one added risk factor for coronary heart disease, such as diabetes, cigarette smoking, and a low level of high-density lipoprotein (HDL cholesterol), or had a history of (but no recent) heart attack or stroke.

ALLHAT participants receive periodic checkups and currently have between 2 and 6 years of followup.

ALLHAT also is comparing chlorthalidone with two other high blood pressure drugs-a calcium antagonist, called amlodipine, and an angiotensin-converting enzyme (ACE) inhibitor, called lisinopril.

About a quarter of ALLHAT's hypertensive patients also are participating in the cholesterol-lowering portion of the study. This includes a fourth of the patients on doxazosin, who will be able to continue their involvement in this aspect of the study.

The cholesterol-lowering study involves older patients with slightly to moderately elevated cholesterol. It is testing whether treatment with dietary changes and an HMG CoA reductase inhibitor, called pravastatin, reduces deaths from all causes better than dietary changes alone.

Other findings about doxazosin in comparison to chlorthalidone are:

Those in the doxazosin group had slightly higher systolic blood pressures than the chlorthalidone group, although the diastolic pressures were the same.

The doxazosin group also had poorer compliance with treatment-only 75 percent were still on the drug or another alpha blocker after 4 years, compared with 86 percent still taking chlorthalidone or another diuretic.

Due to the finding, NHLBI advises high blood pressure patients who now take an alpha-adrenergic blocker drug to consult with their doctors about a possible alternative. If a patient is just starting drug treatment, an alpha-adrenergic blocker may not be the best choice for initial therapy.

"Patients on an alpha blocker for high blood pressure should see their doctor and not just stop taking it," emphasized Dr. Jeffrey Cutler, director of the NHLBI Clinical Applications and Prevention Program and ALLHAT project officer. "We cannot conclude that the drug was harmful. Rather it didn't work as well as the diuretic in reducing cardiovascular disease."

About 50 million Americans have high blood pressure and about 52 million have high blood cholesterol. Both conditions are major risk factors for coronary heart disease and both strike particularly hard at older adults. High blood pressure

also is the chief risk factor for both congestive heart failure and stroke.

Treatment for both high blood pressure and high blood cholesterol typically starts with lifestyle changes, including increased physical activity and weight loss for the overweight. A healthy, low-saturated fat, low-cholesterol eating plan is advised and, for high blood pressure, avoiding excess salt, sodium, and alcohol.

When those changes do not lower elevated blood pressure or cholesterol enough, then drug therapy is needed.

For an interview about ALLHAT, contact the NHLBI Communications Office at (301) 496-4236.

NHLBI press releases, fact sheets, and other materials are available online at www.nhbli.nih.gov

3/7/00

ALLHAT Awareness and Reactions: Wave 1 (US Only)

-Topline Summary-

Prepared for: Pfizer, Inc.
Prepared by: Migliara/Kaplan Associates
Date: March 15, 2000

Methodology

Migliara/Kaplan Associates conducted a total of 41 qualitative depth telephone interviews (teledepths) among a random sample of US physicians, including 18 Primary Care Physicians (PCPs), 11 Cardiologists (Cards), and 12 Urologists (Uros). The interviews were conducted between March 9 and March 15. Each interview was approximately 15 minutes in length.

Due to the qualitative nature of this research, the results that are reported in this document should be considered as "directional in nature" as opposed to statistically conclusive.

Please note that the interviews were not at all intended to inform physicians about any results of ALLHAT. Physicians who were totally unaware of the trial were asked generic questions to satisfy the research commitment on the part of the moderator and the physician.

Summary of Findings

Primary Care Physicians

At this point in time, PCPs' awareness and knowledge of ALLHAT is very low. Of the 18 PCPs interviewed in this research:

- None are aware of ALLHAT on an unaided basis;
- Seven (7) are aware of ALLHAT on an aided basis; and
- Eleven (11) are unaware of ALLHAT.

The PCPs who are aware of ALLHAT have very little knowledge about the trial. In fact, most of the PCPs (5 out of 7) who have heard of ALLHAT only recall the name and nothing else about the trial. Sources of awareness among PCPs aware of the trial include sales representatives, journal articles, and colleagues. These PCPs could not recall which company the drug representatives were selling for or the specific journals. One PCP heard about ALLHAT from a patient who read about the preliminary results in the LA Times.

"I recall the name of the trial, but I do not know anything more about the trial. I think I heard about it from a drug representative, but I cannot recall the name of the drug or the name of the company." (PCP-IM)

"I can remember the name ALLHAT from my journal reading, but I do not know anything about it." (PCP-GP/FP)

Of the two PCPs who have some knowledge of ALLHAT, one PCP only knows that the trial includes patients with hypertension and/or high lipids, and that it is calculating the incidence of cardiovascular events (e.g., heart attacks). However, he does not know what types of drugs are included in the trial. The other PCP is of the understanding that an alpha blocker did not control hypertension as well as a diuretic and that there was a greater risk of CHF among the patients on an alpha blocker.

The one PCP who knows about the negative implication for alpha blockers indicates that he will increase his use of diuretics and calcium channel blockers at the expense of alpha blockers which he uses on a very limited basis for hypertensive patients. However, he will continue to prescribe alpha blockers for the same proportion of BPH patients, with or without hypertension. Currently, of his BPH patients, 95% receive an alpha blocker and 65% specifically receive Cardura.

Cardiologists

Unlike PCPs, Cardiologists' awareness of ALLHAT is relatively high. However, the great majority of the Cardiologists who are aware of ALLHAT know next to nothing about the trial. Of the 11 Cardiologists interviewed in this research:

- Three (3) are aware of ALLHAT on an unaided basis;
- Seven (7) are aware of ALLHAT on an aided basis; and
- Only one (1) is unaware of ALLHAT.

Of the three Cardiologists aware of ALLHAT on an unaided basis, one was an investigator in the trial. The other two Cardiologists read about the trial in a newspaper. All three of these Cardiologists know that Cardura was used in the trial and that because of the results, the agent is being withdrawn from the study. One of these Cardiologists states that concerns about Cardura are mentioned at on-going American College of Cardiology meetings.

"The newspapers mention Cardura. A week ago, I would not have known much about alpha blockers or Cardura. I know now because of all the publicity in the newspapers." (Cardiologist)

Of the seven Cardiologists aware of ALLHAT on an aided basis, five could only recall the acronym from a Cardiology Convention or journal. The other two know that the trial includes drugs used for hypertension, including alpha blockers and diuretics, and that part of the trial is related to the prevention of heart attacks. Generally speaking, the Cardiologists did not seem interested in learning more about ALLHAT and how or if the results would affect their practices.

"I heard about it a few days ago on the radio and on the television news. I am not very interested because it is about alpha blockers and I never use them first line. I do not intend to find out more about the trial." (Cardiologist)

The handful of Cardiologists who are at least somewhat knowledgeable of ALLHAT's preliminary results (three aware on an unaided basis and two aware on an aided basis) do not expect their prescribing to change very much, if at all. Reasons why these Cardiologists do not anticipate changing their habits include:

- Alpha blockers, including Cardura, are not considered first-line therapy anyway; and
- Cardura is still a good add-on for hypertensive patients, particularly those with BPH.

"The data means that you should not use Cardura as first-line therapy. It will not affect my practice because I do not prescribe Cardura first line." (Cardiologist)

"The trial will not affect my use of Cardura. I will still use it with other drugs and it is effective for BPH." (Cardiologist)

Urologists

Urologists' level of awareness of ALLHAT is higher than that for PCPs, but less than that for Cardiologists. Similar to the other specialties included in this research, knowledge of ALLHAT's preliminary results among those aware of the trial is minimal. Of the 12 Urologists interviewed in this research:

- Two (2) are aware of ALLHAT on an unaided basis;
- Four (4) are aware of ALLHAT on an aided basis; and
- Six (6) are unaware of ALLHAT.

Of the two Urologists aware of ALLHAT on an unaided basis, one heard about it at a convention and one received a phone call from a Cardura patient who asked to be switched to another medication. The Urologist who received the call from the patient indicates that he will switch those who ask to Flomax. Both of the Urologists aware of ALLHAT on an unaided basis report that the preliminary results are not very alarming to them because they still consider Cardura to be an effective agent for BPH. However, if the Cardura patients ask to be switched, physicians will likely follow suit.

"Some patients may be hard to convince to take Cardura. I will switch those who ask to be switched." (Urologist)

Of the four Urologists aware of ALLHAT on an aided basis, two only knew the acronym and could not recall anything about it. The other two knew that the trial included alpha blockers, specifically Cardura, and that there were concerns about the likelihood of cardiovascular events among those on the alpha blocker. Sources of awareness cited by these Urologists include lectures, journals, and television news.

"I believe the trial found concerns about congestive heart failure with using alpha blockers." (Urologist)

The Urologists with some knowledge about ALLHAT (about five) do not think the trial or its results have anything to do with BPH. These Urologists will continue to prescribe alpha blockers, including Cardura, for BPH. However, a couple of Urologists report that they will adhere to patients' requests to be placed on a different drug.

"I will prescribe Cardura the same as I always do because I use it for BPH. I believe it will affect family doctors who may use more diuretics and less alpha blockers. It will not affect me." (Urologist)

Conclusions

At this point in time, awareness levels for ALLHAT are very low for PCPs, high for Cardiologists, and moderate for Urologists. However, knowledge of the trial's preliminary results is minimal for all specialties.

- Unaided Awareness: 0 out of 1° PCPs; 3 out of 11 Cards; 2 out of 12 Uros
- Aided Awareness: 7 out of 18 PCPs, 7 out of 11 Cards, 4 out of 12 Uros
- PCPs' awareness and knowledge of ALLHAT are currently so low that it is too early to gauge how the results may affect their practices.
- Cardiologists who are somewhat knowledgeable of ALLHAT's preliminary results do not expect their prescribing patterns to change significantly because they currently do not use alpha blockers as first-line therapy and they still perceive Cardura to be a worthwhile add-on drug for hypertensive patients, particularly those with BPH.
- Urologists who are somewhat knowledgeable of ALLHAT's preliminary results do not anticipate changing their prescribing patterns because they do not believe the findings have anything to do BPH. However, they indicate that they will adhere to patients' requests to be prescribed a drug other than Cardura.

Physicians aware of ALLHAT primarily cite the following sources:

- Television news;
- Newspapers;
- Journals;
- Conferences/conventions; and
- Sales representatives.

Flapan, Valerie

From: Shehu, Migen
Sent: Thursday, March 16, 2000 3:03 PM
To: Helgans, David; Walmsley, Patricia A; Jensen, Dennis M.; Oleksey, Karole M.; Mallen, Sharon; Silber, Beth Ann; Gavigan, Michael; Flapan, Valerie; Cooper, Mark J (Ny-Legal); Natalicchio, Teri
Subject: ALLHAT awareness - US Marketing Research Findings Summary

On March 9-15, Migliara Kaplan conducted 41 qualitative in-depth phone i interviews with 18 PCP's, 11Cardiologists and 12 urologists.
Here is the summary of the results:

At this point in time, awareness levels for ALLHAT are very low for PCPs, high for Cardiologists, and moderate for Urologists. However, knowledge of the trial's preliminary results is minimal for all specialties.

- Cardiologists who are somewhat knowledgeable of ALLHAT's preliminary results do not expect their prescribing patterns to change significantly because they currently do not use alpha blockers as first-line therapy and they still perceive Cardura to be a worthwhile add-on drug for hypertensive patients, particularly those with BPH.

- Urologists who are somewhat knowledgeable of ALLHAT's preliminary results do not anticipate changing their prescribing patterns because they do not believe the findings have anything to do BPH. However, they indicate that they will adhere to patients' requests to be prescribed a drug other than Cardura.

Physicians aware of ALLHAT primarily cite the following sources:

Television news;Newspapers;Journals;Conferences/conventions; and Sales representatives.

Please, find attached the detailed ALLHAT awareness topline findings marketing research for US. A second wave of interviews will be conducted in US and internationally to capture physicians' reaction after the ACC meeting on March 15th.

Best Regards

Migen

ALLHAT-Topline M. Research.doc...

Flapan, Valerie

From: Shehu, Migen
Sent: Monday, March 27, 2000 12:55 PM
To: Helgans, David; Jensen, Dennis M.; Gavigan, Michael; Silber, Beth Ann; Oleksey, Karole M.; Walmsley, Patricia A; Mallen, Sharon; Flapan, Valerie; Cooper, Mark J (Ny-Legal)
Subject: International ALLHAT Marketing Research Update - Awareness remains Low

The ALLHAT awareness study second wave of interviews is being conducted now in US, Italy, UK, Spain and Japan.

While in Spain I had the opportunity to meet and discuss the research with the marketing researchers from all those countries. I informed them on the findings in the USA and got their feedback on the discussion guides. So far they believed the ALLHAT awareness is very low in their respective countries, but it might increase because of competitors'sales reps.

As of Friday, March 24, 2000 ALLHAT international awareness remains low :

Spain
10 of 60 doctors have been interviewed (4 GPs, 2 Cards, 2 Nephs, and 2 Uros)
2 out of the 10 are aware of ALLHAT on an unaided basis (1 Card, 1 Uro)
3 out of the 10 are aware of ALLHAT an aided basis (1 Card, 1 Neph, 1 Uro)
5 out of the 10 are not aware of ALLHAT (4 GPs, 1 Neph)

United States
51 of 60 doctors have been interviewed (19 PCPs, 15 Cards, 17 Uros)
5 out of the 51 are aware of ALLHAT on an unaided basis (2 PCPs, 3 Uros)
18 out of the 51 are aware of ALLHAT an aided basis (6 PCPs, 10 Cards, 2 Uros)
28 out of the 51 are not aware of ALLHAT (11 PCPs, 5 Cards, 12 Uros)

UK

7 out of 60 physicians have been interviewed.
2 out of 7 are aware on an unaided basis.

Japan

The recruiting process is still going on. The one on one interviewing will start soon.

Italy

26 of 60 doctors have been interviewed (13 GPs, 6 Diabetologists, 7 Cards), and NONE are aware of ALLHAT

Best regards

Migen

FROM: Shehu, Migen
TO: Helgans, David; Gavigan, Michael; Silber, Beth Ann; Oleksey, Karole M.; Jensen, Dennis M.; Walmsley, Patricia A; Mallen, Sharon
SUBJECT: Worldwide ALLHAT Awareness Assesment Summary
DATE: 20000419

Please, find attached the Worldwide ALLHAT Awareness Assessment Summary. I'll e-mail it to all the country organizations involved in the research.

Regards

Migen Shehu
7474

BatesFirst: 00000380

BatesLast: 00000398

Att First: 00000379

Att Last: 00000398

SOURCE: CARDURA

ALLHAT Awareness Assessment
-- Marketing Research --

March 2000

CARDURA

Marketing Research Objective and Methodology

- **Objective:**
  - Understand physicians' awareness and initial reaction to the dissemination of ALLHAT preliminary results.
- **Methodology:**
  - In-depth telephone interviews (15 minutes each) with PCPs, Cardiologists, and Urologists and other specialties in different countries conducted by Migliara Kaplan
- **Two Waves of Research:**
  - Wave One (US only) after the NHLBI (National Heart, Lung and Blood Institute) press release, March 8.
  - Wave Two (US, Japan, Spain, Italy, UK) after the American College of Cardiology meeting, March 15.

CARDURA

ALLHAT Awareness Level - US Wave One

US Wave 1	Awareness Level	Unaided Aware	Aided Aware	Unaware	TOTAL
PCPs	Very Low	0% *0 out of 18*	39% *7 out of 18*	61% *11 out of 18*	100% *18 out of 18*
Cardiologists	High	27% *3 out of 11*	64% *7 out of 11*	9% *1 out of 11*	100% *11 out of 11*
Urologists	Moderate	17% *2 out of 12*	33% *4 out of 12*	50% *6 out of 12*	100% *12 out of 12*
TOTAL		12% *5 out of 41*	44% *18 out of 41*	44% *18 out of 41*	100% *41 out of 41*

CARDURA

ALLHAT Awareness Level - US Wave Two

US Wave 2	Awareness Level	Unaided Aware	Aided Aware	Unaware	TOTAL
PCPs	Low	10% *2 out of 20*	30% *6 out of 20*	60% *12 out of 20*	100% *20 out of 20*
Cardiologists	High	0% *0 out of 20*	70% *14 out of 20*	30% *6 out of 20*	100% *20 out of 20*
Urologists	Low	10% *2 out of 20*	15% *3 out of 20*	75% *15 out of 20*	100% *20 out of 20*
TOTAL		7% *4 out of 60*	38% *23 out of 60*	55% *33 out of 60*	100% *60 out of 60*

CARDURA

ALLHAT Awareness Level - Italy Wave Two

Italy Wave 2 [redacted]	Awareness Level	Unaided Aware	Aided Aware	Unaware	TOTAL
PCPs	Very Low	0% *0 out of 20*	0% *0 out of 20*	100% *20 out of 20*	100% *20 out of 20*
Cardiologists	Low	0% *0 out of 20*	10% *2 out of 20*	90% *18 out of 20*	100% *20 out of 20*
Diabetologists	Very Low	0% *0 out of 20*	0% *0 out of 20*	100% *20 out of 20*	100% *20 out of 20*
TOTAL		0% *0 out of 60*	3% *2 out of 60*	97% *58 out of 60*	100% *60 out of 60*

CARDURA

ALLHAT Awareness Level - Spain Wave Two

Spain Wave 2 [redacted]	Awareness Level	Unaided Aware	Aided Aware	Unaware	TOTAL
PCPs	Low	0% *0 out of 20*	20% *4 out of 20*	80% *16 out of 20*	100% *20 out of 20*
Cardiologists	Moderate	15% *2 out of 13*	7% *1 out of 13*	77% *10 out of 13*	100% *13 out of 13*
Urologists	Low	0% *0 out of 12*	17% *2 out of 12*	83% *10 out of 12*	100% *12 out of 12*
Nephrologists	Low	7% *1 out of 15*	7% *1 out of 15*	87% *13 out of 15*	100% *15 out of 15*
TOTAL		5% *3 out of 60*	13% *8 out of 60*	82% *49 out of 60*	100% *60 out of 60*

CARDURA

ALLHAT Awareness Level - UK Wave Two

UK Wave 2	Awareness Level	Unaided Aware	Aided Aware	Unaware	TOTAL
PCPs	Moderate	0% *0 out of 22*	32% *7 out of 22*	68% *15 out of 22*	100% *22 out of 22*
Cardiologists	High	10% *1 out of 10*	60% *6 out of 10*	30% *3 out of 10*	100% *10 out of 10*
Urologists	Moderate	0% *0 out of 11*	36% *4 out of 11*	64% *7 out of 11*	100% *11 out of 11*
Diabetologists	High	40% *4 out of 10*	30% *3 out of 10*	30% *3 out of 10*	100% *10 out of 10*
Geriatricians	High	17% *2 out of 12*	67% *8 out of 12*	17% *2 out of 12*	100% *12 out of 12*
TOTAL		11% *7 out of 65*	43% *28 out of 65*	46% *30 out of 65*	100% *65 out of 65*

First Wave US Findings are Optimistic

CARDURA

- **PCPs -** Too early to predict anything about their Cardura prescribing behavior following ALLHAT's preliminary results.
- **Cardiologists -** Do not expect to change their prescribing patterns significantly because:
  - Currently they do not use alpha-blockers as first-line therapy.
  - Worthwhile add-on for HTN patients, particularly those with BPH.
- **Urologists -** Do not expect to change their prescribing patterns. They believe:
  - The findings have nothing to do with BPH.
  - However, they will switch to Flomax upon patient request.

CARDURA

Second Wave US Findings: A Few Physicians Switch to Flomax

- **PCPs** - Those PCPs with awareness are cautious about prescribing Cardura:
  - Many PCPs request more information on trial results.
  - A few now prefer Flomax, or will switch to Flomax upon patient request.
- **Cardiologists** - Expect they will use less ABs and more ACE Inhibitors because:
  - ABs, including Cardura, still reserved for patients with BPH.
  - ABs are not used as first line therapy for HTN.
- **Urologists** - Expect to change somewhat their prescribing behavior in the future:
  - Although they will continue to prescribe ABs for patients with BPH, they will switch from Cardura to Flomax upon patient request.

Second Wave US Findings: A Few Physicians Switch to Flomax

- *"I'll increase the use of diuretics and CCB at the expense of AB, however I'll continue to prescribe AB the same way as before for BPH." (PCP, US, 1st wave)*
- *"I probably will use an alpha blocker on somebody with isolated hypertension without co-morbid conditions or probably for patients with hypertension and prostate problems." (CARD, US, 2nd wave)*
- *"If I get information that there is actually a risk involved, I will obviously go to an alternative. Probably Flomax...it does not have as many side effects as Hytrin..." (URO, US, 2nd wave)*

CARDURA

Second Wave Spain Findings: No Changes in Prescribing, Yet Overall Awareness is Low

- **PCPs** - Too early to predict changes in prescribing behavior.
- **Cardiologists** - Do not expect to change prescribing behavior significantly since:
  - Will continue to prescribe Cardura for BPH patients.
  - Cautious approach to preliminary results of ALLHAT.
- **Urologists** - Too early to predict changes in prescribing behavior.
- **Nephrologists** - Too early to predict changes in prescribing behavior.

CARDURA

Second Wave Italy Findings: Physicians Have Little or No Awareness of ALLHAT Results; No Changes Predictable

- **PCPs** - Too early to predict changes in prescribing behavior.
- **Cardiologists** - Too early to predict changes in prescribing behavior. However, significant impact on prescribing behavior is not expected as:
  - CARDs generally do not attribute importance to use of ABs for HTN and BPH.
  - "Alpha blockers in general are suitable either for hypertension or for BPH, but I think this is mostly applicable only for patients over 60." (CARD)
- **Diabetologists** - Too early to predict changes in prescribing behavior. However, ABs are typically third line therapy after ACE Inhibitors and CCBs.

Second Wave UK Findings: Some Changes in Prescribing

CARDURA

- **PCPs** - No changes in prescribing behavior, yet too early to predict future changes in prescribing.
- **Cardiologists - Currently reducing use of ABs and Cardura in particular:**
  - For some CARDS, ABs are becoming "agents of last resort" to treat HTN based on safety concerns.
  - Yet a minority of CARDs will continue to prescribe Cardura for patients with HTN and BPH, based on Cardura's ability to interact with other agents.

CARDURA

Second Wave UK Findings: Some Changes in Prescribing

- **Urologists -** No changes in prescribing behavior, yet too early to predict future changes in prescribing.
- **Diabetologists -** Reducing use of ABs due to safety concerns.
  - Cardura becomes "second line or third line status" for treatment of HTN.
- **Geriatricians - Cautiously reducing use of ABs based on safety concerns.**
  - Reduction for newly diagnosed HTN patients.
  - Cardura will continue to be used for patients with HTN and BPH.

CARDURA

Second Wave UK Findings: Some Changes in Prescribing

- *"It will reduce my doxazosin prescribing practice. Essentially, I am now cautious...I now use it less often." (CARD, UK, 2nd wave)*
- *"It probably will have an effect on prescribing...feeling is that ACE inhibitors will come out on top." (CARD, UK, 2nd wave)*
- *"I won't run away from alpha blockers, but I'll need to take a closer look..." (GERI, UK, 2nd wave)*

Second Wave Japan: Market Research Still in Field

- Results expected by April 24-25

CARDURA

Sources of Information on ALLHAT, in Order of Importance

US Wave One: Television News, Newspapers, Journals, Conferences, Patients, Sales Reps

US Wave Two: Sales Reps, Journals, Conferences, Newspapers, Patients, Colleagues, Internet

Spain Wave Two: Conferences, Journals, Colleagues, Internet

Italy Wave Two: Journals, Colleagues

UK Wave Two: Sales Reps, Journals, Conferences, Colleagues, Internet

CARDURA

Summary - Overall Awareness is Low

- There is a vagueness pertaining to the ALLHAT preliminary results knowledge. Aided awareness is much higher that unaided one.
- English-speaking countries (US, UK) have highest awareness of ALLHAT results since:
  - Easier access to information sources
  - Sales reps more active than in non-English speaking countries
- Some US physicians (especially CARDS and UROs) are somewhat cautious:
  - Reduced use of Alpha Blockers; Increased use of ACE Inhibitors
  - Upon patient request, some switching from Cardura to Flomax
  - Cardura still reserved for patients with HTN and BPH.

Summary

CARDURA

- Some UK physicians (especially CARDS and DIABs) are beginning to change prescribing behavior based on safety concerns:
  - Alpha Blockers becoming class of "last resort" to treat HTN.
  - Geriatricians cautious but also expect to reduce use of ABs.
  - PCPs and UROs have not changed behavior to date.
- Spain and Italy: Too early to predict changes in prescribing behavior

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF NEW YORK

LAWRENCE D. BERNHARDT,)
Plaintiff,)
vs.) 00 CIV 4042 (LMM)
PFIZER, INC.,)
Defendant.)
---)
ARNOLD LIEBMAN,)
Plaintiff,)
vs.) 00 CIV 4379 (LMM)
PFIZER, INC.,)
Defendant.)

MONDAY, OCTOBER 23, 2000

2:15 p.m.

Deposition of LAWRENCE R. KRAKOFF, M.D., held at ENGLEWOOD HOSPITAL AND MEDICAL CENTER, 350 Engle Street, Englewood, New Jersey 07631, before SUZANNE J. DRUGA, a Certified Shorthand Reporter (License No. 1845) and Notary Public of the State of New Jersey.

A. It's quite small. It's fairly small. I really couldn't be sure. Five percent maybe.

Q. What percentage of the roughly 20 percent of the patients who are maintained on a single drug are taking an alpha-blocker?

A. Probably none at the present time.

Q. And has that changed over the last year?

A. Yes.

Q. Is that change following the ALLHAT study, the release of the data from the ALLHAT?

A. I would have to say there weren't very many to begin with, but it certainly did.

Q. When you say "there weren't very many to begin with", prior to the change that was in place after the information from ALLHAT was released, approximately what percentage of your 20 percent of patients on a single drug were on an alpha-blocker?

A. It probably was about the same as the ones on a calcium blocker only in the past two or three years. And I really can't give you exact figures.

Q. I understand.

A. But to be honest with you, certainly in the last two or three years as evidence has accumulated, I have shifted more patients over to ACE inhibitors; or if they can't tolerate them, to ARB's, angiotensin receptive blockers, as monotherapy in most cases.

Q. And of the patients who were taking an alpha-blocker as their sole means of therapy --

A. I would have to say I can't remember that there were many patients who I started on alpha-blocker and monotherapy; others did. And there are studies written, and I have reviewed some which I thought were pretty good for our journal which I published few years ago. It was kind of interesting, but I just never change my habits one might say, I guess partly because ALLHAT had already planned and I thought it would be interesting to see how it came in.

Q. Of those patients who were taking alpha-blockers before these ALLHAT study results were released, and I understand we said this is a very small number, how many of those were taking Cardura as an alpha-blocker?

A. Almost all I would guess. Since it

patients who are considered refractory hypertensive as one of the most frequent reasons to refer to me, and so that may be as much as 40 percent.

Q. And of these 80 percent or so total patients, how many of them --

A. When you say 80 percent, I'm not sure what you mean.

Q. If you take everyone who is not on a single drug.

A. Well, there are two other more.

Q. 80 percent of the patients who are on two or more antihypertensives, currently how many of your patients are taking Cardura?

A. Well, it's probably only men, with the rare exception there may be a woman who has responded especially well and is still on it, so and of those I'd say probably 20, 30 percent.

Q. Has that number changed at all over the last year?

A. It's been reduced a little bit since ALLHAT, but it's only since April that ALLHAT had been out, although the report came out earlier, but that is the presentation. So I guess it's gone down by a few patients wherever I would say

it's on an individual basis, but felt that we could probably discontinue with it and see how they did with regard to their prostate symptoms, was there an alternative, did they really need it, and their blood pressure.

I have to say if there were multiple drugs and we decided to discontinue the Cardura and in fact it turned out that their blood pressure was best controlled on Cardura, in that setting I would resume that. And there have been such cases that I can remember.

(Whereupon a short break was taken.)

(Whereupon Exhibit No. D-4, Article from the Journal of the American Medical Association on April 19, 2000, entitled, Major Cardiovascular Events in Hypertensive Patients Randomized to Doxazosin versus Chlorthalidone, The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), was marked for identification.)

Q. We've marked as Defendant's Exhibit 4 an article that appeared in the Journal of the American Medical Association on April 19, 2000 entitled Major Cardiovascular Events in Hypertensive Patients Randomized to Doxazosin

I do think that given the information available from ALLHAT, that physicians should consider their patients and are their patients predisposed to heart failure and might they make a better choice, and that's on an individual basis, if I were asked. If you asked me as a referring doctor, I have a patient in this situation, do you think I should switch from Cardura to something else, I would try to put it that way.

Q. Is it your opinion, Doctor, that Cardura is doing something affirmative which leads to heart failure?

A. Well, I think this is such an interesting finding in a large, a big trial with a lot of patients in it, that that really deserves some good research to figure out why this might be so, and I'd like to see it.

Q. Referring you to Exhibit 5, which is your NIH press release.

MR. GRAZIANO: I have it somewhere.

(Discussion held off the record.)

Q. Now, I don't know where it shows up on yours, but towards the end of the press release there is a quote from Dr. Jeffrey

Cutler. The paragraph begins "Patients on an alpha-blocker for high blood pressure should see their doctor and not just stop taking it." Do you see that quote?

A. Uh-huh.

Q. Yes?

A. Right, I see that.

Q. And after identifying Dr. Cutler it says, quote, "We cannot conclude that the drug was harmful", end quote. Are you familiar with that statement by Dr. Cutler?

A. Well, I am reading it.

Q. Do you have any evidence from which you can conclude that the drug was harmful?

A. I don't disagree with Dr. Cutler. I think that there isn't sufficient information, research studies or anything I'm familiar with to disagree with him. I think he is as knowledgeable as anyone. I respect his opinion a great deal. And we discuss issues, we know each other. And I think that is a fair assessment on the basis of the information available up to now.

And I think though that there is something that isn't mentioned, and that is,

earlier experience with prazosin, an alpha-blocker, in heart failure studies was quite discouraging because it was thought that prazosin would be effective in heart failure. And compared to other treatments, and these are older studies, it turns out that the alpha-blocker prazosin was short acting to be sure, but was actually associated with a worse outcome in heart failure patients than the other treatments it was compared with.

Q. And again, that wasn't a placebo-controlled trial?

A. This is an old heart failure study that Dr., I can't remember which one it was, but Dr. Cohen and Dr. Packer I think were involved with or wrote about, and I haven't really looked at it again. I didn't think it helped much in this situation of treating hypertensives. But it's some evidence that alpha-blockers have yet to be shown to have any special benefit in cardiovascular disease based on the clinical trial data, so no special benefit, and in this study a worse outcome compared to the diuretic. And that's where we are. And it seems to me someone should be looking into this further.

discussions, and others have questioned what's the best thing to do. And it's sort of a consensus among doctors about it, that we pretty much all agree about the same thing, the ones I've talked to.

Q. What is that consensus?

A. What was stated in the article, that its use is to be confined to multidrug patients who seem to be refractory to everything else and they respond especially well. And then the issue of prostatic hypertrophy, I think we are little uncomfortable with it. And for men who are hypertensive and have prostatic hypertrophy as monotherapy. And I don't see many of those, but I think some urologists do and probably some family practitioners do, I don't know, I mean there's a lot that one doesn't know as to whether there are alternatives and whether to use alpha-blocker therapy for those patients, whether Flomax is really better than -- for some reason it's less -- it causes less trouble. And no one knows these things, so it's just a little bit of a worry, because if one takes from this study, the implication that maybe it would be better if you use this little alpha-blocker and use them as

infrequently as possible and maybe just limit it to combinations would be best. So this is uncharted.

Q. Have you had any communications with anyone at Pfizer regarding the ALLHAT study?

A. No, I haven't.

Q. Have you had any discussions with anyone at Pfizer regarding Cardura?

A. No.

Q. Have you had any discussions with anyone at FDA regarding Cardura?

A. No, I haven't.

Q. Have you had any discussions with anyone at FDA regarding the ALLHAT study?

A. The FDA regarding the ALLHAT study?

Q. Yes.

A. No, I haven't.

Q. Have you made any requests to the FDA or any other body to send notice out to physicians nationwide regarding ALLHAT?

A. No, I haven't.

Q. Are you aware of anyone else who's made such a request to the FDA or a regulatory body, other than the plaintiffs in this case?

A. No. I have to say I don't recall

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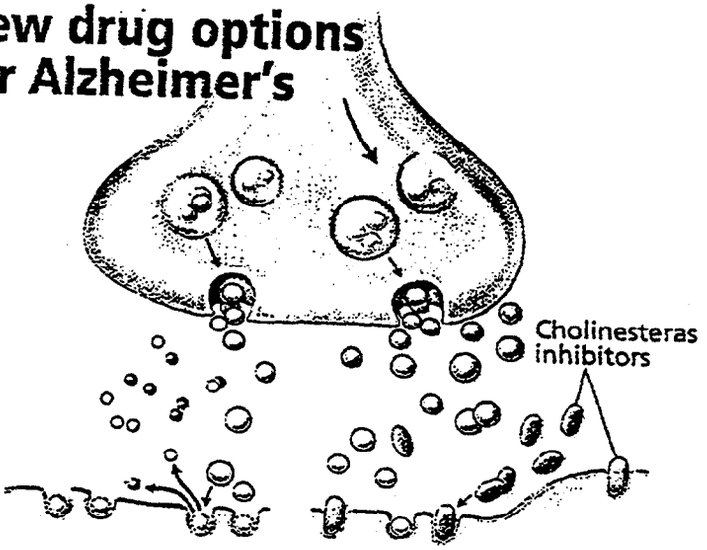

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COMPLETE TABLE OF CONTENTS PAGE 386

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DONALD G. VIDT, MD*
Consultant, Department of Nephrology and Hypertension, Cleveland Clinic; member, Sixth Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; investigator, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)

Alpha-blockers and congestive heart failure: Early termination of an arm of the ALLHAT trial

ABSTRACT

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) is a large, randomized double-blind study comparing four antihypertensive agents (chlorthalidone, doxazosin, amlodipine, and lisinopril) in hypertensive patients older than 55 years. The doxazosin arm was terminated early, when the trial's safety and monitoring board noted a twofold higher incidence of congestive heart failure in patients receiving doxazosin than in those receiving chlorthalidone (8.13% vs 4.45% at 4 years, $P < .001$).

ALPHA-ADRENERGIC BLOCKING AGENTS (alpha-blockers) will likely be removed from the list of first-line antihypertensive drugs, in light of surprising findings from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT): an incidence of congestive heart failure twice as high among patients receiving the alpha-blocker doxazosin (Cardura) than among those receiving the thiazide diuretic chlorthalidone (Thalitone, Hygroton, and generic preparations).[1]

Confronted with these findings, the Director of the National Heart, Lung, and Blood Institute (NHLBI) stopped the doxazosin arm of the study, although the other arms comparing chlorthalidone with the angiotensin-converting enzyme inhibitor lisinopril (Prinivil, Zestril) and the calcium antagonist amlodipine (Norvasc) will continue for 2 more years.

Although these findings seem to argue against the use of doxazosin as a first-line antihypertensive, they do not address the drug's appropriateness in combination therapy. Further, the study did not examine the use of doxazosin as an adjunct in treating elevated cholesterol or benign prostatic hyperplasia.

ALLHAT should serve as a reminder that we should not measure the effectiveness of antihypertensive drugs only by their effects on surrogate markers such as blood pressure or serum cholesterol levels. Moreover, to assess the effect of therapy on the "hard" end points that really matter—morbidity and mortality—we will need to continue to conduct large-scale, long-term trials.

Current guidelines will need to be changed

WHAT IS THE BEST FIRST-LINE ANTIHYPERTENSIVE AGENT?

Hypertension significantly increases the risk of cardiovascular morbidity and mortality. A series of classic randomized clinical trials, culminating approximately 10 years ago, proved that diuretics and beta-blockers lower this risk (although fewer trials were conducted with beta-blockers than with diuretics).

Since those trials, several new classes of agents—calcium antagonists, angiotensin-

*Disclosure: The author has indicated that he has received grant or research support from the Searle, Astra-Zeneca, and Novartis companies and serves on the speakers' bureaus of the Astra-Zeneca, Merck, Novartis, and Solvay companies, all of which make antihypertensive agents.

converting enzyme (ACE) inhibitors, alpha-blockers, and angiotensin II antagonists—were approved and became popular. A trial using "hard" clinical end points found a calcium antagonist to be superior to placebo,[2] and other trials suggested that the other classes were equivalent to diuretics or beta-blockers in efficacy.[3–5]

Are the newer agents truly as good as the older ones? Many experts believed they would be even better. After all, diuretics and beta-blockers without intrinsic sympathomimetic activity raise serum cholesterol levels, whereas the new drugs do not—and alpha-blockers actually lower cholesterol. Diuretics lower serum potassium and magnesium levels and increase blood glucose levels; the new drugs do not—and the alpha-blockers actually improve insulin sensitivity. Diuretics lower blood pressure by volume depletion (at least in the short term), whereas the new drugs work by vasodilation, which is more physiologically correct. Some of the new drugs (such as ACE inhibitors) also have more of an effect on left ventricular hypertrophy. Thus, many of the new classes of antihypertensive drugs appear to have mechanisms of action and beneficial effects apart from blood pressure-lowering that would make them better than the older agents.

But trials were needed to find out, and one such trial was ALLHAT, which began enrollment in February 1994. Follow-up will continue until March 2002.

■ ALLHAT STUDY DESIGN

Sponsored by the NHLBI, the ALLHAT study is a randomized, double-blind, active-controlled comparison of four antihypertensive agents[6]:

- Chlorthalidone (a diuretic; 12.5 to 25 mg/day)
- Doxazosin (an alpha-blocker; 2 to 8 mg/day)
- Amlodipine (a calcium antagonist; 2.5 to 10 mg/day)
- Lisinopril (an ACE inhibitor; 10 to 40 mg/day).

In addition, approximately one fourth of the ALLHAT patients are also participating in a randomized, open-label trial to determine whether lowering serum low-density lipoprotein cholesterol levels with an HMG-CoA reductase inhibitor (pravastatin) reduces all-cause mortality compared with a control group receiving usual care.

Patients

Patients are men and women age 55 and older with hypertension (systolic blood pressure ≥ 140 mm Hg, or diastolic blood pressure ≥ 90 mm Hg, or currently taking antihypertensive medication) plus at least one additional risk factor for coronary heart disease, including previous myocardial infarction or (MI) stroke, left ventricular hypertrophy by electrocardiogram or echocardiogram, type 2 diabetes mellitus, current cigarette smoking, or a low level of high-density lipoprotein cholesterol.

A total of 42,448 patients were recruited and randomized, 15,268 to receive chlorthalidone, 9,067 to receive doxazosin, and the rest to receive the other drugs.

The baseline characteristics in the chlorthalidone and doxazosin groups (which were well matched) were as follows:

- Mean age: 67 years
- Women: 47%
- Black: 35%
- Mean blood pressure: 145/83 mm Hg
- Being treated for hypertension: 90%
- Atherosclerotic vascular disease: 45%
- Type 2 diabetes: 36%
- Smokers: 22%
- Mean serum creatinine level: 1.0 mg/dL
- Mean serum cholesterol level: 216 mg/dL.

Outcomes measured

Predefined outcomes measured were the incidences of:

- Coronary heart disease (the primary outcome, including both coronary death and nonfatal MI)
- All-cause mortality
- Stroke
- "Combined coronary heart disease" (coronary death, nonfatal MI, revascularization procedure, and hospitalization for angina)
- "Combined cardiovascular disease" (coronary death, nonfatal MI, stroke, revascularization, angina, congestive heart failure, and peripheral arterial disease).

TABLE 1

4-Year outcomes from ALLHAT: Chlorthalidone vs doxazosin

OUTCOME	4-YEAR RATE (%)		RELATIVE RISK IN DOXAZOSIN GROUP	95% CONFIDENCE INTERVAL	P VALUE
	CHLORTHALIDONE GROUP (N=15,268)	DOXAZOSIN GROUP (N=9,067)			
Coronary heart disease*	6.30	6.26	1.03	0.90–1.17	.71
All-cause mortality	9.08	9.62	1.03	0.90–1.15	.56
Combined coronary heart disease†	11.97	13.06	1.10	1.00–1.12	.05
Stroke	3.61	4.23	1.19	1.01–1.40	.04
Combined cardiovascular disease‡	21.76	25.45	1.25	1.17–1.33	< .001
Congestive heart failure	4.45	8.13	2.04	1.79–2.32	<.001
Coronary revascularization	5.20	6.21	1.15	1.00–1.32	.05
Angina	10.19	11.54	1.16	1.05–1.27	<.001
Peripheral artery disease	2.87	2.89	1.07	0.88–1.30	.50

*Fatal coronary heart disease and nonfatal myocardial infarction
†Fatal coronary heart disease, nonfatal MI, revascularization procedure, and hospitalization for angina
‡Coronary heart disease death, nonfatal MI, stroke, coronary revascularization procedure, angina (treated in hospital or as outpatient) congestive heart failure (treated in hospital or as outpatient), and peripheral arterial disease (in-hospital or outpatient revascularization)

ADAPTED FROM THE ANTIHYPERTENSIVE AND LIPID-LOWERING TREATMENT TO PREVENT HEART ATTACK TRIAL (ALLHAT). MAJOR CARDIOVASCULAR EVENTS IN HYPERTENSIVE PATIENTS RANDOMIZED TO DOXAZOSIN VS CHLORTHALIDONE. JAMA 2000; 283:1967–1975.

■ ALLHAT STUDY RESULTS: DOXAZOSIN STUDY STOPPED

As in all major clinical trials, an advisory committee periodically reviews the safety of the ALLHAT. Following independent data reviews on January 6 and January 21, 2000, the director of the NHLBI accepted a recommendation to stop the doxazosin treatment arm. The median follow-up was 3.3 years at that point.

The finding that prompted this decision? Compared with patients in the chlorthalidone group, patients in the doxazosin group had:

- A 25% higher incidence of "combined cardiovascular disease" ($P < .001$)
- Twice the incidence of congestive heart failure ($P < .001$).

These higher incidences were approximately the same in all subgroups studied: patients both older and younger than 65 years, black and nonblack, men and women, Hispanic and non-Hispanic, and with or without diabetes mellitus.

On the other hand, there were essentially no differences in the rates of fatal coronary heart disease or nonfatal MI (the primary outcome) or all-cause mortality between the two treatment groups (TABLE 1),[1] and there were only small trends toward more events in the doxazosin group for the other outcomes.

Another reason for stopping the doxazosin arm of the study: At that point, about 61% of the coronary heart disease events that had been expected to occur in the chlorthalidone group had already occurred. The investigators calculated that there was only a 1% chance that doxazosin would eventually prove to be more beneficial than chlorthalidone by the end of the trial, based on the protocol-specified alternative hypothesis of a 16% reduction in coronary heart disease events.

Blood pressure lowering is only a surrogate endpoint

■ TRIAL RAISES QUESTIONS

The ALLHAT findings raise a number of questions to which, at present, we have no answers.

Do alpha-blockers cause heart failure, or just prevent it less?

Unfortunately, it is not possible to determine whether the incidence of congestive heart failure with doxazosin observed in ALLHAT is the same as, less than, or more than would be expected without antihypertensive treatment.

What caused the differences?

There are several theories but no definitive answer.

Doxazosin lowered systolic blood pressure less. At 1 year, the mean blood pressure was 140/79 mm Hg in the doxazosin group and 137/79 mm Hg in the chlorthalidone group. At 4 years, the numbers were 137/76 vs 135/76 mm Hg.

But could a difference of 2 to 3 mm Hg in systolic blood pressure explain the differences in end points? Several recent trials in older patients[2,5,7] suggest that 3 mm Hg could explain a 10% to 20% increase in congestive heart failure, but not the doubling of risk observed in ALLHAT. Similar calculations for stroke and angina from earlier trials[8,9] (using diuretics and beta-blockers) suggest that 3 mm Hg could explain most of the differences in stroke or angina events observed in ALLHAT.

The study did not address the use of doxazosin to treat BPH

Also of interest: more people stopped taking doxazosin than chlorthalidone. At 4 years, 86% of patients assigned to chlorthalidone were still taking a diuretic, while 75% of those assigned to doxazosin were still taking an alpha-blocker. With both drugs, symptomatic side effects were the number-one reason for stopping, followed by "unspecified refusal."

Alpha-blockers may affect left ventricular hypertrophy less. Left ventricular hypertrophy (LVH) is a common precursor of heart failure. As yet we have no data on the effect of the different agents on LVH in ALLHAT, but previous studies[10–12] suggested that alpha-blockers may affect LVH less than do diuretics.

Alpha-blockers may have adverse biochemical effects, increasing plasma volume[13] and possibly increasing plasma norepinephrine levels.[14] The significance of these effects is unknown.

■ RECOMMENDATIONS

On the basis of the ALLHAT observations, it would seem appropriate to recommend that doxazosin not be used as monotherapy in managing stage 1 or 2 hypertension (ie, 140–179/90–109 mm Hg).

This means changing the guidelines. For example, the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure[15] recommends diuretics and beta-blockers for initial monotherapy of uncomplicated hypertension, but also recommends other classes of agents, including alpha-blockers, if there are specific indications for them—benign prostatic hyperplasia or dyslipidemia in the case of alpha-blockers. Treatment guidelines from several other countries include similar recommendations.

ALLHAT did not address the many patients who receive doxazosin as part of combination therapy for hypertension. It may be appropriate to continue using doxazosin for patients who are also receiving a diuretic and possibly other classes of antihypertensive agents concurrently. Patients who are taking an alpha-blocker as part of combination therapy may wish to discuss the issue of continuing this therapy with their physicians.

Similarly, this study did not address the use of doxazosin (or other alpha-blockers) as an adjunct to treat elevated cholesterol or benign prostatic hyperplasia in normotensive patients. Continued use of these agents in these conditions appears appropriate, except perhaps in the early stages of heart failure, ie, in patients with mildly or moderately decreased systolic function. Given that other classes of drugs are available to treat hypertension, elevated cholesterol, and benign prostatic hyperplasia, it may be reasonable to avoid alpha-blockers in this situation, although we have no data.

■ CONTINUED NEED FOR LARGE TRIALS

Antihypertensive agents are traditionally approved on the basis of how well they lower blood pressure. It is assumed that lowering blood pressure will reduce morbidity and mortality regardless of the agent used, and clinical

trials have supported this notion. As a consequence, blood pressure has long been used as a surrogate end point to predict the rate of cardiovascular outcomes such as MI, stroke, and all-cause mortality.

ALLHAT suggests some modification in this notion. Different antihypertensive agents can have different physiologic effects—which we may not even be aware of—that can add up to differences in morbidity and mortality. And the only way to find out about these effects is to conduct large studies to assess morbidity and mortality. ■

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FOR IMMEDIATE RELEASE
March 15, 2000

AMERICAN COLLEGE OF CARDIOLOGY ISSUES CLINICAL ALERT ON THE USE OF ALPHA BLOCKERS FOR HYPERTENSION

ACC Recommends that Physicians Reassess Use Based on New Findings

(ANAHEIM, CALIF.)-The American College of Cardiology (ACC) recommends that physicians discontinue use of a widely prescribed drug, an alpha-adrenergic blocker, for the treatment of hypertension. This recommendation follows announcement of the results of a large high blood pressure study today at the ACC 49th Annual Scientific Session in Anaheim, Calif. Approximately 50 million Americans have hypertension, or high blood pressure.

The study was halted last week by the study sponsor, the National Heart, Lung, and Blood Institute (NHLBI), due to data showing that the alpha blocker, doxazosin (Cardura®), is less effective than the more traditional diuretic in reducing some forms of cardiovascular disease, such as congestive heart failure. The study, Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), showed that users of doxazosin had 25 percent more cardiovascular events and were twice as likely to be hospitalized for heart failure than users of the diuretic chlorthalidone.

According to the NHLBI, of the 24 million Americans who take medication to treat their hypertension, about one million use an alpha blocker. "The ACC encourages physicians who treat hypertensive patients to review the new data with their colleagues to ensure the rapid dissemination of this important information," said Dr. Robert J. Cody, chair of the ACC Hypertensive Diseases Committee and associate chief of the Cardiovascular Division at the University of Michigan Medical School in Ann Arbor. "At the same time, hypertensive patients taking an alpha blocker should first see their physicians before discontinuing its use. This is important because the treatment of hypertension and the choice of medication should be individualized for each patient."

The results were presented at the ACC meeting by Dr. Curt Furberg, of the Wake Forest University School of Medicine in Winston-Salem, N.C., and Dr. Barry Davis, of the University of Texas School of Public Health in Houston.

For more information about the ALLHAT study, go to www.nhlbi.nih.gov and go to "news" and "press releases."

The American College of Cardiology, a 25,000-member nonprofit professional medical society and teaching institution, is dedicated to fostering optimal cardiovascular care and disease prevention through professional education, promotion of research, leadership in the development of standards and guidelines, and the formulation of health care policy.

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF NEW YORK

LAWRENCE D. BERNHARDT, Plaintiff, vs. PFIZER, INC., Defendant.	00 CIV 4042 (LMM)
ARNOLD LIEBMAN, Plaintiff, vs. PFIZER, INC., Defendant.	00 CIV 4379 (LMM)

DEPOSITION OF JAMES L. POOL, M.D.

New York, New York

Monday, October 30, 2000

Reported by:
TAMI H. TAKAHASHI, RPR
JOB NO. 6568

project.

Q. The money that's being paid to Baylor College of Medicine, do you have any interest in that money?

MS. LESKIN: Objection. Vague.

Q. Let me ask a different question.

Will you be entitled to receive the money that is paid to Baylor College of Medicine?

A. No.

Q. Have you ever worked with Pfizer in the past?

MS. LESKIN: In any capacity?

MR. GRAZIANO: Any capacity.

A. Worked for them -- explain what that means.

Q. Work with them either in cases such as this or even research projects.

A. Absolutely.

Q. Can you tell me about that experience.

A. My first interaction with Pfizer Pharmaceuticals in the United States began in the third quarter of 1982 when they came to the Baylor College of Medicine and solicited our input into the development of a new compound.

Pool

And that new compound was Doxazosin, subsequently, marketed in the United States as Cardura, C-A-R-D-U-R-A, subscript registration sign.

And, at that time, Joan Leader, L-E-A-D-E-R was a Ph.D. who had the responsibility at the Groton, Connecticut facility, the research laboratories of Pfizer, to identify the direction for development and identify the appropriate human research protocols for this new compound.

And so in December of 1982, we went forward jointly with applying for an all new drug application to Ray Lipicky at the NIH. And we were granted that and began the human research studies in the United States on Doxazosin.

Q. How long did those studies last?

A. It's been ongoing to the present. 17 years.

Q. How much of your time has been spent working on those studies over the course of the 17 years, in percentage term?

A. Total percent of time spanning 17 years, less than 1 percent.

Pool

Q. Do you know whether or not Pfizer awarded a grant to Baylor College of Medicine or this specific group with regard to the in vitro research project?

A. They did.

Q. Do you know how much that was?

A. No, I do not.

Q. Okay. Do you expect this type of research to continue in the future, that is, research concerning Doxazosin?

A. I do. I can't tell you exactly what direction it's going to go.

Q. Do you expect future grants from Pfizer to support this research?

MS. LESKIN: Objection. Calls for speculation.

Q. If you know.

A. I think future research initiatives have really meaningful scientific imperative that we will anticipate will be funded.

Q. From Pfizer?

MS. LESKIN: If you know.

A. From Pfizer.

Q. Do you consider your relationship with

Pfizer to be important?

MS. LESKIN: Objection. Vague.

Q. You can answer.

A. I guess you have to define important.

Q. Okay.

A. What's important mean?

Q. That's fair enough. I'll ask you a different question.

Would you personally like to maintain the relationship with Pfizer?

A. Yes.

Q. Why?

A. Because it has been very open and supportive of a number of very important research initiatives in cardiovascular medicine, cardiovascular pharmacology, which is like many of the other industries as well as governmental agencies that we deal with.

Q. In this case, you've been retained by Pfizer to be an expert witness, correct?

A. Correct.

Q. Have they ever retained you in that capacity before?

A. No.

talking about, do you know if you were ever qualified as an expert witness?

A. In all those cases, yeah.

Q. Was there ever a case where you worked in -- either concerning these four or even others that we haven't mentioned -- where you were not accepted as an expert witness?

A. No.

MR. GRAZIANO: I want to mark this as Pool No. 1.

(Plaintiff's Exhibit 1, Curriculum Vitae of James Lewis Pool, M.D., marked for identification, as of this date.)

Q. I have in front of you what's been marked as Pool No. 1. I believe it's a copy of your CV. Why don't you look at that and tell me whether or not that's correct?

A. That is correct.

Q. On page 9 of the Exhibit No. 1, four entries up from the bottom, there's a lecture in Phoenix, Arizona which it was entitled, "first-line Therapy" -- actually, I'm sorry. I'm on the wrong page. Just give me a second.

Look at page 9 and four from the

bottom, San Juan, Puerto Rico.

A. Um-hum.

Q. International symposium entitled, "The Role of Doxazosin in Lipid Metabolism." Do you see that?

A. I do.

Q. Was this a lecture you gave?

A. Yes.

Q. What did that lecture concern?

A. It was a description of my research on Doxazosin and other alpha1-adreoceptor antagonists and their impact and the mechanism of that impact on the metabolism of lipoproteins.

Q. Did that research receive any support from Pfizer, if you know?

A. The two supporting agencies for that research was the -- was Pfizer, Abbott Laboratories and one government agency which was the National Institutes of Health.

Q. You described Pfizer as a supporting agency. Does that mean they contributed money in terms of a grant for the research?

A. Correct.

Q. Do you know how much money was

contributed?

A. That research was done prior to 1988, and I don't remember.

Q. Okay. Let's take a look at the next page. On page 10 of Exhibit 1, the second entry from the top, Naples, Florida, National Symposium, "Effects of Doxazosin on Serum Lipids." Do you see that?

A. Correct.

Q. What did that presentation concern?

A. Same body of data. As you'll notice, one was an international presentation in April and one was a national presentation in September.

Q. Okay. So the same body of data, does that mean it came from the same research project?

A. That's correct.

Q. And let's move on to the next one. Page 15 of Exhibit 1. Let's see, three down there's an entry regarding Japan. It's called "The Second International Symposium On Multiple Risk Factors In Cardiovascular Disease."

And then skipping a few words there's a part in quotes called "Effects of Doxazosin in Hypertensive Patients on Lipids, Platelets

and" --

A. Thrombolysis.

Q. -- "Thrombolysis." Thank you. What did that presentation concern?

A. That presentation included all of lipid research from our laboratory up through that time, plus additional research that we performed on the effect of Doxazosin on platelet aggregation and thrombolysis. Thrombolysis is the term that describes the dissolution, the breakup of intravascular blood clots.

Q. The additional research you performed, was that supported by Pfizer in any way?

A. It was.

Q. Was that in the form of a grant?

A. Yes.

Q. Do you recall how much that grant was?

A. No.

Q. Let's take a look at page 22 of Exhibit 1. Now, on this page, we're no longer talking about presentations, correct?

A. Correct.

Q. Are these published articles, is that what this is a list of?

Pool

MS. LESKIN: This particular page?

MR. GRAZIANO: Yes, page 22.

A. Page 22 is a part of a list of abstracts, scientific abstracts, published somewhere in the world.

Q. Okay. Let's look at the one that's marked No. 32.

A. Um-hum.

Q. What does that abstract concern?

A. That, actually, would be, in abstract form, a brief summary of the scientific data that you saw as part of the public or scientific presentations in the earlier discussion of San Juan Puerto Rico, United States, et cetera. So it would, actually, be the print form of that scientific data.

Q. Okay. What about No. 33, what did that abstract concern?

A. That -- this abstract is my analysis of Pool data from an international series of studies, United States, including largely our data, Europe and Australia and the Asian countries, looking at the clinical effects of Doxazosin on lipids and lipoproteins.

Q. Okay. The work involved in preparing this abstract, was it sponsored by Pfizer in any way?

A. It was.

Q. Do you recall how much -- I'm sorry. Was that in the form of a grant?

A. It -- there were multiple, multiple grants to all the countries involved, all the investigators involved, correct.

Q. When you say "multiple, multiple grants," were they all from Pfizer, the grants?

A. I cannot answer that. I don't know.

Q. Was more than one of them from Pfizer?

A. Certainly, they must have been.

Q. Did you receive any from Pfizer concerning this abstract?

A. Nothing additional beyond the original grants that generated the data that went into the abstract.

Q. I see. The abstract marked No. 34, what did that concern?

A. That's a presentation of the same data that you see in abstract 33 with, at the time of the presentation, a little bit more information

because we, in fact, had a little more time between the two.

Q. Were there any additional grants you received in preparing the abstract listed in No. 34?

A. No.

Q. Let's take a look now at page 27 of Exhibit 1. This page, I believe, by looking at page 25, consists of a list of published papers; is that correct?

A. That is correct. These are complete manuscripts.

Q. The manuscript listed under No. 16 --

A. Yes.

Q. -- can you briefly summarize what that concerned?

A. This is the full manuscript, full description of the work that we had talked about earlier, the beginning of the work on the effect of Doxazosin on lipid metabolism in humans. And it was published in this journal as the date indicated 1987.

Q. What about the one listed under No. 19, what did that concern?

Pool

A. That, again, is additional data. In this particular publication, we had gone on and done, on another level, a little bit more sophisticated level of laboratory analysis with regard to the mechanisms of how Doxazosin impacted on lipid metabolism.

Q. That additional laboratory analysis, was that sponsored by Pfizer in any way?

A. It was.

Q. Do you recall how much money was received from Pfizer for that additional analysis?

A. I do not.

Q. The next page. Actually, skipping that page. The following page, page 29, the entry listed under No. 38, can you briefly describe what this concerned?

A. The title of this manuscript is, "Effects of Doxazosin on coronary heart disease risk factors in the hypertensive patient." And this is a summary of the known antiatherogenic effects of Doxazosin on various parameters, including systolic blood pressure, diastolic blood pressure, lipoproteins,

platelets, left ventricular hypertrophy and other factors that contributes to coronary heart disease.

Q. This study, was it sponsored by Pfizer in any way?

A. Some of the data in here are a direct result of Pfizer grants and contracts to the Baylor College of Medicine, and some not.

Q. The grants and contracts, do you recall how much they were?

A. No.

Q. Okay. What about the manuscript listed in No. 39, what did that concern, briefly?

A. 39 is a manuscript that deals with the role of the sympathetic nervous system in the clinical entity called LUTS, which is lower urinary tract syndrome and what we used to call prostatism or the symptoms associated with benign prostatic hyperplasia.

And it describes the mechanism by which the sympathetic nervous system promotes male symptoms with benign prostatic hyperplasia and the potential role of alpha-adrenoceptor blockade in reversing those symptoms and

Pool

And, at the same time, they did not see that in the Amlodipine or Lisinopril arm.

And that the -- for unknown reasons, they were seeing an increase in cardiovascular morbid events in the Doxazosin arm greater than in the Chlorthalidone arm.

Q. In your opinion, do those findings have any implications for the treatment of hypertension?

MS. LESKIN: Just to clarify, any implication?

MR. GRAZIANO: Yes.

A. Well, the answer to that is yes.

Q. And what would the implications be?

A. Well, the ALLHAT trial is focused on a group of high risk patients. Those high risk patients, if you use the terminology of the joint national committee on prevention detection, evaluation and treatment of high blood pressure, would stratify the ALLHAT patient population as a Group C risk factor group.

I think the ALLHAT trial demonstrates that that particular patient population is a population that the Doxazosin group -- Doxazosin

Pool

treatment recommendations for Group C patients does not change, correct?

A. The treatment recommendations for Group C patients are to lower their blood pressures to less than 130 over 85 millimeters of mercury, which is not something that you can accomplish with monotherapy. Even the monotherapy in the majority of those patients is the recommended first and second drugs of choice in many cases.

Q. Would the interim ALLHAT findings have any implications for investigating the group of drugs to be given to Group C either as monotherapy or add-on therapy?

A. We don't know about the add-on monotherapy because the ALLHAT doesn't actually address that issue.

Q. So, at this point, would you make any changes to add-on therapy as a result of the interim ALLHAT findings?

A. No, because we don't have -- the data doesn't speak to that.

Q. Okay. So it's fair to say, in your opinion, the treatment of Group C patients does

not change following the ALLHAT findings?

A. I think that's -- I think that is correct, yeah.

Q. And the treatment of Group A and B patients does not change either?

A. That's correct.

Q. Okay. I want to show you what I'm going to mark as Pool No. 2.

MR. GRAZIANO: Why don't you mark this as Pool No. 2.

(Plaintiff's Exhibit 2, Letter to the editor in Lancet, marked for identification, as of this date.)

Q. I'm now showing you what's been marked as Pool No. 2. It's a two-page document, but my concern only focuses on the first page.

A. Okay.

Q. And the first question is, the first page of Exhibit No. 2, do you recognize this document?

A. Yes, I do.

Q. What is this document?

A. This is a letter to the editor or what's called commentary in Lancet, March the

Pool

11th of 2000 by Franz Messerli.

Q. Do you know who Franz Messerli is?

A. Yes.

Q. Who is he?

A. Franz Messerli is an internist that practices at the Ochner Clinic, New Orleans.

Q. Have you worked with him professionally in the past?

A. Yes.

Q. In what capacity?

A. As a colleague in the field of hypertension, cardiovascular diseases. He is, in fact, the editor of one of the textbooks that I have a chapter in.

Q. The Lancet, what is that?

A. The Lancet is a medical journal.

Q. I want to focus specifically on something that Franz Messerli said in this commentary, and that's in the last full paragraph on page 1, the paragraph that starts out, "What are the consequences of the decision to discontinue the Doxazosin arm of ALLHAT?" Do you see that paragraph?

A. Yes.

Pool

Q. Okay. The third sentence of that paragraph says, "All five of these guidelines will have to be amended to the effect that Doxazosin, or the whole class of peripheral alpha-blockers, should no longer be considered as first-line antihypertensive therapy." Do you see where I'm reading?

A. I certainly do.

Q. Do you agree with Franz Messerli in that regard?

A. No, I do not.

Q. What is your belief?

MS. LESKIN: Can you be a little more specific?

MR. GRAZIANO: Okay. Yes, I'll change the question.

Q. Why did you disagree with him?

A. I think if you reflect upon the date that this was published, you will be aware that this opinion was rendered and published before the author, in fact, saw even the preliminary results of the ALLHAT trial.

So it's hard for me to understand how one could formulate an opinion about the ALLHAT

trial, and certainly such sweeping recommendations as you see in the sentence that you highlighted, without actually looking at the data.

Q. Have you ever communicated with Franz Messerli regarding this commentary?

A. No.

Q. So it's fair to say you never told him you disagree with the sentence I just highlighted?

A. That is correct.

Q. The next sentence right after the one that I highlighted says, "Whether Doxazosin should continue to be used as add-on antihypertensive therapy remains to be determined." Do you see that sentence?

A. Yes, I do.

Q. Do you agree with that sentence?

A. Remains to be determined, no. I --

Q. What is your belief?

A. My belief is that it remains an effective add-on therapy for the reduction of blood pressure, because that has been clearly demonstrated in add-on therapy trials.

Pool

And the -- but the focus there is exactly that, we have data to show that it's effective in reducing blood pressure when it's added on to other antihypertensive therapy. It does not address any other questions.

Q. Is there a split in the medical community regarding the two sentences that I just read to you? In other words, do some persons in your position believe what you believe and do others believe what Franz Messerli believes?

A. Yes.

MS. LESKIN: Objection. Vague.

Q. Do you know if you, yourself, are in the minority or the majority in terms of the split?

MS. LESKIN: Objection. Vague. You can answer.

Q. You can answer, if you can.

A. To know whether you're in the not minority or the majority, you have to have both the numerator and denominator. And I'm -- I can't make that calculation. I don't know.

Q. And another way of asking the same question -- your answer may be the same -- is, do

Pool

Lessons from ALLHAT."

Do you see the article?

A. I see this one.

Q. Do you recognize the document?

A. Yes.

Q. What is the document?

A. It's an editorial that accompanied the report from the ALLHAT steering committee on the withdrawal of Doxazosin arm from the ALLHAT trial.

Q. The author of the editorial appears to be Louis Lasagna, M.D. do you know who that person is?

A. I know him by name.

Q. What do you know about him, just generally speaking?

A. He is a senior physician who has been involved in academic medicine for many, many years. A major area of his impact, at least in the public press, has been in the area of antibiotics and therapeutics related to antibiotics.

Q. On the second page of the document, the second column, the first full paragraph, the

very first sentence there says, "The decision to discontinue the Doxazosin arm of this trial has important implications. First, the assumption that the most important parameter in treating hypertension is lowering blood pressure, rather than the drug which blood pressure is lowered, is challenged" --

MS. LESKIN: "With which,".

Q. I'm sorry. -- "with which blood pressure is lowered, is challenged substantially by these results."

Do you see the two sentences that I just read?

A. Yes, I do.

Q. I believe the answer was yes, Doctor?

A. I see those, um-hum.

Q. Would you agree with those first two sentences?

A. I agree with the first sentence. I have a concern about what the author might be implying with the second sentence.

Q. What do you think he might be implying with the second sentence?

A. Well, my concern about the second

sentence is that he can interpret from, again, the preliminary data what the secondary end points of this trial imply.

Q. Well, do you believe that's what he's doing, or he's raising a concern about the use of the drug Doxazosin to lower blood pressure?

MS. LESKIN: Objection. Calls for speculation.

Q. If you have a belief either way.

MS. LESKIN: To the extent you understand.

A. Based on the data from the trial, there was no difference at the end of the four years in the diastolic blood pressure. And there was a 2 to 3 millimeter difference in mean blood pressure, in the systolic blood pressure. Obviously, that does raise a concern.

It means that, although it seems like 2 to 3 millimeters of mercury is incredibly trivial, when you apply that across thousands of patients, it can, in fact, have a very significant impact on some outcomes. And the one that you would mention immediately would be stroke.

Pool

Q. What about the fact that there was a doubling of the likelihood of congestive heart failure, do you think that could have been caused by the 2 or 3 points, I believe you said?

MS. LESKIN: Objection, vague. And objection, misstates the evidence.

Q. You can answer.

A. Based on everything that we know to date about congestive heart failure in hypertensives with the high risk for ischemic heart disease, it's not reasonable to assume that the 2 to 3 millimeters of systolic blood pressure difference and higher values in the Doxazosin group compared to the diuretic group would explain the difference in heart failure.

Q. Is it possible that there was something else about the drug Doxazosin that's yet unknown that could have caused the difference?

MS. LESKIN: Objection. Vague.

A. That's one of several possibilities.

Q. The last sentence in this paragraph that we're looking at says, "Finally, these results have major implications for the

recommendations for treatment of hypertension, which currently include Doxazosin as a first-line agent."

Do you see that?

A. Yes.

Q. Would you agree with that sentence?

A. I would not agree with that sentence.

Q. Why not?

A. Again, the implication of that sentence is that the author is mixing fruits. He's mixing apples and oranges in the sense that what the study has demonstrated is that Doxazosin is not superior to diuretic. And that, in a high risk patient group, so-called risk Group C, that Doxazosin should not be chosen as a superior antihypertensive.

Those are the people that were being studied. It's a -- I mean, it's a great disappointment to us in clinical medicine, because there were many of us, and as you can see from my CV, I would be listed among them -- I mean, I have to face the harsh reality that -- of what ALLHAT says, that is that all of the clinical hypotheses that we put forth, we could

A. Yes.

Q. Okay. I want to look at the second page of this document. Three paragraphs up from the bottom of the page, it says, "Due to the finding, NHLBI advises high blood pressure patients who now take an alpha-adrenergic blocker drug to consult with their doctors about a possible alternative. If a patient is just starting drug treatment, an alpha-adrenergic blocker may not be the best choice for initial therapy."

Do you see that paragraph?

A. I do.

Q. Would you agree with that paragraph?

A. Well, I think the problem with that is the sweeping nature of it, because that's certainly not what the thought leaders in the field are telling the practicing physicians to do.

Q. When you say "thought leaders in the field," are you referring to the same dozen or so people you were referring to earlier?

A. Yes.

Q. Can you name those people?

Pool

Q. The third paragraph of this press release on page 175 says, "In its official statement, which follows, the ACC Hypertensive Diseases Committee urged patients taking an alpha blocker to see their physicians for reassessment."

Do you see that?

A. Yes.

Q. Would you agree that patients taking an alpha-blocker should be urged to see their physicians for reassessment following the ALLHAT interim findings?

A. I would, because for the very reason that we have talked about, that those patients should ascertain whether or not, first and foremost, that their blood pressure is properly controlled. And the second is that their regimen is, basically, in compliance with what we know from the ALLHAT trial.

Q. Okay. I want to look at a different portion of this same document. I just got to see if I can decide from my notes here for a moment. Okay, yes.

Going back two pages to the page

marked 173 -- and, actually, just so you have the full picture, 173 appears to be part of a presentation that begins at the very first page of this document that's page 169 and goes through 173. So why don't you just briefly scan those few pages.

A. You want me to begin with --

Q. The very first page.

A. 170?

Q. Yes, 170 or 169 which appears to be the title page. What you're looking for, by the way, is an answer to the question, have you ever seen this summary before.

A. I have not seen this --

MS. LESKIN: Take a look.

A. -- summary before. It appears to be a summary from the oral presentation at the American College of Cardiology.

Q. The oral presentation you just referred to that referred to the ALLHAT interim findings, correct?

A. Correct.

Q. You were aware before today that there was an oral presentation?

A. That is correct.

Q. And that that presentation was made sometime in March of this year?

A. In Anaheim, California at the annual convention. They were actually scheduled to present this after I presented, that's correct.

Q. You were there?

A. I was a presenter, yes. I was on program.

Q. Did you stay for that presentation?

A. I was not. In fact, it was on a different day and I had returned to Houston.

Q. You are aware, nonetheless, this presentation was made?

A. Correct.

Q. Okay. Have you ever seen this summary of the presentation before?

A. I have not, I have not.

Q. Okay. On the page marked 173, that's about three pages into it, the very last sentence in that page says, "Until proven otherwise it seems prudent to at least assume that Doxazosin is also inferior as a second or third line hypertensive agent and the long-term

cardiovascular safety of alpha-blockers and BPH should be investigated."

And those remarks appear to be attributed, if you look at the very previous page at the top of 1723, to Dr. Curt Furberg.

A. Correct.

Q. Okay. Going back to 173, assuming for the moment those remarks were actually made by Dr. Curt Furberg, would you agree with them?

A. No.

Q. Why not?

A. First, I think he certainly has become confused, because have we pointed out what the ALLHAT trial was designed to do?

Q. Yes.

A. It was designed to show that it was superior to Chlorthalidone. When you fail to show superiority, it does not mean that you are equal and it does not mean you're inferior.

Q. You are aware that he was the chairman of the steering committee for ALLHAT, correct?

A. Yes.

Q. Actually, he still has that role today?

A. Yes, he does.

Q. Nonetheless, you believe he was confused regarding the interim findings of ALLHAT?

A. No. I think he's confused with his use of the term.

Q. Which term would that be?

A. The inferior. The sentence that you pointed out to me, "Until proven otherwise it seems prudent to at least assume that Doxazosin is also inferior," also implying that it's inferior. But his own study proves that, in fact, it's not superior.

Q. Other than him being confused, do you think it's possible that you and him just have a disagreement as to the implications of the study?

A. That's possible.

Q. But your belief today is more that he is misunderstanding the implications of the study in which he's a chair, correct?

MS. LESKIN: Objection.

Q. You can answer.

A. No. I think he's misusing the word. And I'm not sure that, you know, given an

opportunity to rephrase that sentence, that, in fact, he would keep it in that format.

Q. I see. Have you ever discussed his use of that word with him?

A. No, I haven't.

Q. Okay. Just give me a moment. I want to show you an affidavit that Dr. Curt Furberg prepared and signed in this case.

MR. GRAZIANO: We'll have this affidavit marked as No. 6.

(Plaintiff's Exhibit 6, Affidavit of Dr. Curt D. Furberg in Support of Plaintiffs' Application for an Order to Show Cause, marked for identification, as of this date.)

Q. In front of you is Pool No. 6, which is an affidavit that Dr. Curt Furberg prepared in this case. Have you ever seen this affidavit before?

A. I have seen this just today.

Q. Let's look at the paragraph No. 7 which starts on the bottom of page 3 of Dr. Furberg's affidavit. The last sentence of paragraph 7 on page 3 says, "Pfizer's delay in

providing such notification may every year cause thousands of unnecessary cases of heart failure among the large number of hypertensive patients who currently use Cardura."

Do you see that sentence?

A. I do.

Q. Would you agree with that sentence?

A. No.

Q. Why not?

A. Dr. Furberg's own data from ALLHAT does not show a cause and an effect relationship between the drug and the heart failure.

Q. And do you believe that, in paragraph No. 7, he's talking about cause and effect as opposed to a correlative relationship?

MS. LESKIN: Objection. Calls for speculation.

Q. If you know.

A. Could you explain to me what the difference is between a cause and effect and a correlative relationship?

Q. I'll try my best. In other words, could Dr. Furberg be saying in paragraph No. 7, the sentence we've just been focusing on, that

Pool

was an ALLHAT study and it did release some interim findings in March of 2000?

MS. LESKIN: Objection, as no clarification as to the source of that notification.

Q. Regardless of the source.

A. The doctors, through all of the communications of major events, they are, in fact, well aware of acronym identified, major clinical trials. They know it's a part of the science of evidence-based medicine. They look for these trials, they know that these trials are coming. They're not a big surprise to them, because we -- ALLHAT has been talked about for five years.

And I think a poll of American physicians would -- you would have a reasonable number of physicians that would recognize the ALLHAT trial. And they're certainly not going to recognize the implications of the ALLHAT trial because the implications to the ALLHAT trial are not a consensus position. The one thing we know is that, in Group C risk factor patients, Doxazosin is not superior to diuretic for the

treatment of high risk hypertensives.

Q. What would be a reasonable number of doctors who would recognize it, in your opinion?

MS. LESKIN: Objection. Vague.

MR. GRAZIANO: It's his words.

MS. LESKIN: It's your question. And I think it's vague.

Q. Go ahead. You can answer.

A. I would hope that the majority of primary care physicians, and let's say those are general practice physicians, internists and gynecologists, including obstetrics and gynecology because their primary care responsibility is for women on many occasions, and to a certain extent pediatrics, they're usually the four groups in the primary care, that those groups, the majority of those physicians have heard about ALLHAT. And, in fact, probably have some sense of even the controversy about ALLHAT.

Q. Okay.

MS. LESKIN: Is your answer concluded, Doctor? Did you finish your answer?

THE WITNESS: Yes.

Q. You just used the words hope, and I wanted to distinguish that from any current belief you may have. Is that your present belief, that the majority of primary care physicians have knowledge of ALLHAT, or is that just your hope?

A. It's, actually, an unscientific sample.

Q. And the unscientific sample, does that lead you to have a belief or a hope?

A. A belief.

Q. A belief, okay.

And do you believe, based on the same unscientific sample, that the majority of primary care physicians had knowledge of ALLHAT even prior to the March 2000 release of the interim findings?

A. No. The number of physicians who are now aware is substantially greater than before the ALLHAT findings were announced in the public press, as well as the scientific press, because some physicians are only interested in results rather than announcements of trials being underway.

Pool

The other thing that makes the ALLHAT trial significant is its tremendous distribution throughout the nation. You, in fact, have a group of ALLHAT investigators in a vast array of communities in this country that are actually recognized. They're known to be ALLHAT investigators. They have been talking about what's been going on. You know, the ALLHAT trial is doing this, the ALLHAT trial is doing that. We have three more years of ALLHAT, four more years of ALLHAT, et cetera. So it's not -- by virtue of its vastness, it has permeated the practice community because that's where the ALLHAT investigators are. It's a community-based study.

Q. Before, you mentioned the word poll. I just want to confirm, you yourself haven't conducted any polls?

A. I have not done scientific polls. What I was referring to is standing in front of primary care physicians prior to the release of the ALLHAT interim findings, how long, 1995 to the present.

I have been personally presenting the

ALLHAT trial to physicians as one of the major trials that is under way in the field of hypertension, a part of a body of clinical trials that number 250,000 patients in total. That will be coming up, you know, bit by bit, item by item that will need to digest and will need to make additional recommendations to them.

And I've been doing that for five years. And since the first of the year, people are asking me for my interpretations, my conclusions of the preliminary results of ALLHAT during this interim analysis.

Q. Okay. And based on that experience, you believe that the majority of primary care physicians have knowledge of the ALLHAT findings?

A. Being defined as 51 percent or more.

Q. 51 percent or more, okay.

Do you know whether or not Pfizer conducted any polls of the type that you described?

A. I'm not aware of any polls by anybody on the knowledge of primary care physicians about ALLHAT.

Q. I want to show you what I believe is a

poll conducted by Pfizer. Let me get that.

MR. GRAZIANO: No. 7.

(Plaintiff's Exhibit 7, Poll conducted by Migliara/Kaplan Associates, marked for identification, as of this date.)

Q. In front of you has been a document that's been marked Pool No. 7. It has the Bates range 05009934 through 9941. It actually appears to be a compilation of at least three different documents. Why don't we start with the very first page of the document.

MS. LESKIN: Sal, if I could, just for the record, this document, Exhibit 7, as well as Pool Exhibit 5, come from Pfizer's files and have been marked confidential. And under the parties' confidentiality order, the court reporter is required to be informed and Dr. Pool is required to be informed that these documents have been marked as confidential and not to be used outside the scope of this litigation.

MR. GRAZIANO: Thank you. I appreciate that.

Q. No. 7, I assume this is a document you

have not seen before?

A. That's correct.

Q. The title of the document says, "ALLHAT Awareness and Reactions Wave 1 (U.S. Only)."

Do you see that?

A. Yes.

Q. Then it says, "Prepared for: Pfizer, Inc., Prepared by: Migliara/Kaplan Associates." Do you see that?

A. I do.

Q. Do you know who they are, Migliara/Kaplan Associates?

A. No, I don't.

Q. Have you ever heard of them?

A. No, I haven't.

Q. Okay. Then halfway down the first page there's something called "Summary Of Findings, Primary Care Physicians."

"At this point in time, PCP's awareness and knowledge of ALLHAT is very low. Of the 18 PCPs interviewed in this research:

"None are aware of ALLHAT on an unaided basis.

Pool

"Seven are aware of ALLHAT on an aided basis; and.

"11 are unaware of ALLHAT."

Do you see that?

A. Yes.

Q. Would that portion of the document, assuming it's correct, change in any way your unscientific opinion that 51 percent or more of primary care physicians are aware of ALLHAT?

A. I'm glad to inform you that my sample size is about 10 orders of magnitude bigger than this one.

Q. So the answer is that this one doesn't change your unscientific opinion?

A. Doesn't change my opinion.

Q. Okay.

A. I stand in front of audiences that number in the hundreds to, more recently, in the thousands, including the American Academy of Ophthalmology in Dallas. I have 18 people on a row, not 18 people in a survey.

Q. The next paragraph on the same first page, the last paragraph on the page says, "The PCPs who are aware of ALLHAT have very little

knowledge about the trial. In fact, most of the PCPs, (5 out of 7) who have heard of ALLHAT only recall the name and nothing else about the trial."

Once again, that would be inconsistent with your experience, correct, Doctor?

A. May I ask for clarification?

Q. Yes.

A. Do you know or can you ascertain from the document when the document -- when the survey was done relative to the ALLHAT disclosure --

Q. On --

A. -- the full disclosure?

Q. On the top of the document, there's a date which is March 15, 2000. Do you see that?

A. I see that.

Q. So let's assume for the moment that the study was done on or about that time.

A. Let me see. When -- when did -- when was the public disclosure, as it were, to the American College of Cardiology? Do you have the date?

Q. Yes. I'm going to show you a document that may help.

A. Let me look at my Palm Pilot and I'll have the date I spoke at American College of Cardiology.

Q. Why don't you do that and we'll use that date for the moment.

A. I opened American College of Cardiology on -- I was in the first day and that -- I believe the first day of that was March the 11th of 2000.

Q. Okay. Why don't we go back.

MS. LESKIN: Can he finish his answer, please.

Q. Do you have anything else to add?

A. Well, do you understand what I'm commenting on?

Q. Absolutely.

A. Is that the time -- if they did the presentation at the American College of Cardiology on the 16th and this is a document dated the 15th, then this would -- one would assume that someday before the 15th they did the survey. And so this survey, in fact, was between March the 9th and March the 15th.

Q. Okay. Well, let's stop for a minute.

A. Okay.

Q. For the record, your counsel pointed to a portion of the document. You were in the middle of stating an assumption, but then you gave a specific date.

A. Yeah.

Q. That time range, March 9th through March 15th, that's not an assumption. It's based on what the document now says in the first full paragraph, correct?

A. Yes.

MS. LESKIN: Just to clarify, the document, which is Exhibit 7, the last line of the first paragraph says, "interviews were conducted between March 9 and March 15."

Q. Let's go back to the NHLBI press release marked earlier today as Exhibit No. 4. That press release, if you go back to Exhibit No. 4, was dated March 8th of 2000. Do you see that?

A. That is correct.

Q. So let's now assume that the survey referred to in Exhibit No. 7 was conducted within

the first week after the issuance of the NHLBI press release. With that assumption in mind, does -- do the results of this survey presented on the first page of Exhibit No. 7 change your opinion regarding how many primary care physicians were aware of ALLHAT?

A. No, because my opinion is based upon my own personal direct interaction with physicians that, as I said, is at least 10 orders of magnitude greater than this. So I can't comment upon this methodology or who -- how they contacted those people or how they paid them or anything else. There's just a difference of opinion here.

Q. You are aware of the use of statistics in sampling, correct?

A. Correct.

Q. You didn't attempt to do any scientific studies yourself regarding the awareness of primary care patients of the ALLHAT?

A. I did not.

Q. You have no basis today to testify scientifically as to how many physicians are aware of ALLHAT versus how many are not?

Pool

A. I do not.

Q. Okay. I want you to look at the page of this same document, Exhibit No. 7, marked 938. Tell me if you find that page.

A. I have page 938.

Q. Okay. At the top of that page, there's a section called "Conclusions" and I'll read to you the paragraph I want you to focus on, which is, "At this point in time, awareness levels for ALLHAT are very low for PCPs, high for Cardiologists, and moderate for Urologists. However, knowledge of the trial's preliminary results is minimal for all the specialties."

Do you see that?

A. Yes.

Q. Assuming that conclusion to be true for the moment, would that have been different from your belief?

A. Yes.

Q. And how would it have been different?

A. My -- my interaction with the primary care physicians, again, defined as family practice, internal medicine, obstetrics, gynecology and pediatrics, which would be

significantly higher than these numbers.

Q. Now, we were talking before about the fact that these numbers were apparently conducted in telephone interviews between March 9th and March 15th.

A. Right.

Q. Do you believe that, based on your unscientific experience, that awareness levels would have increased after March 16th, the date of the conference we were talking about?

A. Because of public information?

Q. Yes.

A. Right.

Q. Do you believe it would have increased?

A. It should have.

Q. Okay. Let's take a look now at a page of this same document, Exhibit 7, marked 940, ending in 940.

A. Okay.

Q. We're looking now at what appears to be an E-mail, which I believe you have not seen in the past; is that correct?

A. That is correct.

Q. There is, on the top third of the way down, a bold sentence that appears on this document. It's also underlined. And it says, "As of Friday, March 24th, 2000, ALLHAT international awareness remains low."

Do you see that?

A. Yes.

Q. Assuming that that statement is true, would that be inconsistent with what your belief would be? Based on your unscientific experiences, you believe that is considerably different?

A. Yes.

Q. Okay. There is an entry for the United States right under Spain. Do you see that?

A. Yes.

Q. The last sentence of that entry says that, "28 out of the 51 are not aware of ALLHAT," and in parentheses it says, "11 PCPs, 5 Cards, 12 Uros."

Do you see that?

A. Yes.

Q. Okay. Would that be inconsistent with

your belief?

A. That is correct.

Q. Okay. Do you have any beliefs about other foreign countries' awareness levels such as Spain or U.K. or Japan or Italy, or is that beyond your unscientific experience?

MS. LESKIN: Objection. Because it's beyond the scope of this lawsuit.

Q. You can answer.

A. Actually, I presented the ALLHAT trial results in Tokyo.

Q. Okay.

A. So I've had a chance to talk to the Japanese about it.

Q. With any of these other foreign countries listed here? The reason I say that, there's no answer for Japan. If you see what it says under Japan, it says, "The recruiting process is still going on", so I was wondering if you had any personal experience, unscientific or not, regarding Spain or Italy or the U.K.?

A. No.

Q. Okay. Going back to Exhibit No. 7 for the moment, do you know of any reason why Pfizer

would have requested Migliara/Kaplan Associates to prepare the survey that's evidenced in the document?

MS. LESKIN: Objection. Calls for speculation.

Q. If you know.

A. I do not know.

Q. Okay.

MR. GRAZIANO: Mark this No. 8, please.

(Plaintiff's Exhibit 8, E-mail dated 2000/4/19, from Shehu to distribution list, marked for identification, as of this date.)

Q. Now I'm showing you what's been marked as No. 8. It's another document marked confidential for the record. This has the Bates range 05 000712 through 732. I do not believe this is a document you have previously seen, but why don't you take a look at it.

A. I have not seen this document before.

Q. Actually, let's start with the third page of the document for a moment. It's the one that has the bottom number 715.

MS. LESKIN: The fourth page?

Pool

MR. GRAZIANO: The fourth page, I'm sorry. 715 on the bottom.

A. Okay. I have that page.

Q. Okay. The last entry on this page says, "Two Waves of Research," "Wave One (U.S. only) after the NHLBI press release, March 8th. Wave Two, "U.S., Japan, Spain, Italy, U.K., after the American College of Cardiology meeting, March 15th."

The American College of Cardiology, March 15th, that's the same meeting you were referring to earlier where you had an unrelated presentation, correct?

A. That's correct.

Q. Let's now look at two more pages into the document, the one that ends in 717. Assuming the information on this page is accurate, I understand you have not seen it before, under U.S. Wave 2, which I'll ask you to assume took place after the American College of Cardiology meeting, specifically for PCPs, which I'll ask you to assume stands for primary care physicians, the document indicates that 60 percent or 12 out of 20 primary care physicians were unaware of the

ALLHAT study. Do you see where I'm referring to?

A. Yes, um-hum.

Q. Those findings would be inconsistent with your unscientific experiences regarding awareness of ALLHAT; is that correct?

MS. LESKIN: Objection. Asked and answered.

Q. Okay.

A. That's correct.

Q. The entry for Urologists, just on the same page, shows a 75 percent unawareness. And again, that level of unawareness, assuming it's been accurately computed for the purposes of this document, would be inconsistent with your unscientific experiences of awareness levels of ALLHAT, correct?

A. Correct.

Q. One thing I haven't asked you so far, I will now, I assume you've been retained in this case by Pfizer -- I'm sorry -- your college has been retained in this case by Pfizer for you to provide certain expert opinions; is that correct?

A. Correct.

Q. What are those opinions?

leading the pack in terms of their knowledge about ALLHAT.

Q. Okay. What percentage of those types of physicians, cardiologists, do you think should know about the interim ALLHAT findings --

MS. LESKIN: Objection.

Q. -- in the ideal world?

MS. LESKIN: Objection. Calls for speculation, hypothetical.

Q. You can answer the question.

A. Hypothetically, we want every physician to know the body of data that is critical for the care of any patient that's in front of them. Now, that's the ideal world. Beyond that ideal number, you can -- it's everybody's opinion as to what we can accomplish.

Q. The ideal number would be 100 percent, then?

A. Certainly.

Q. Now, what about primary care physicians, what would the ideal number of primary care physicians who should know about the ALLHAT interim findings be, in your opinion?

MS. LESKIN: Objection. The question

is vague.

Q. You can answer.

A. In a very theoretical sense, it relates specifically to the patients who, in fact, would be Group C risk factor hypertensives who a primary care physician might treat with monotherapy.

Q. So can you put a percentage number on it or not?

A. I mean, I can't -- it's hard for me to speculate on what percentage of --

Q. Would you agree with me that an ideal number of primary care physicians who had knowledge of ALLHAT's interim findings would also be 100 percent?

A. It would be ideal.

Q. Let's go now to Exhibit C which is the previous page in the Furberg affidavit.

MS. LESKIN: Let's clarify. Exhibit of C of Exhibit 6?

MR. GRAZIANO: Pool Exhibit 7.

THE WITNESS: No. 6.

MR. GRAZIANO: It's 6?

MS. LESKIN: 6.

the core issues that we've just talked about before this document, just as the document to the physician is trying to reemphasize the JNCVI recommendations for treatment of a particular subgroup of patients.

Let's say that, for example, you send this to every hypertensive in the United States who is taking Cardura, knowing full well that even the presumed implications, let alone the known data about the ALLHAT trial, focuses on that population, shall we broadly say 20 percent. So we're going to send out to 80 percent of the people a document that applies to Group C, but there's actually Group A and B that ALLHAT doesn't address.

I'm not sure that it's in the best interest of the patient to raise questions which really don't have any import to them.

Q. Would it be in the best interest of the patient to consult with their physicians to reassess their use of Cardura, given ALLHAT's findings?

A. If they, in fact, are Group Cs, it actually could be very valuable because it

could -- the ALLHAT trial -- and even the questions about Doxazosin in the ALLHAT trial actually can be -- could be very valuable for the Cs to refocus physicians and their patients on what we really know.

Q. So, at least, for the Group C population, this notice could cause something that would be in the patient's best interest, and that is a consultation with their doctors, correct?

MS. LESKIN: Objection. Misstates the testimony.

Q. You can answer.

A. Well, I guess the issue is, we're in hopes that every hypertensive is getting usual and customary care for their blood pressure and somebody is documenting, first, that they're taking their medications and, second, that their blood pressure is under control. And you can't do that without making a physical -- being physically present in a physician's office, some doctor or healthcare provider of that physician.

So that one would assume that, under usual and customary medical care, that the

FROM:	Oleksey, Karole M.
TO:	Heiman, Cees J.; Lee, Albert; Lim, Eng-Khong Nick; Orlina, Carmencita T; Tohma, Yoshinori; Katen, Karen L; O'Connor, Hugh; Read, Ian C; Schleier, Dudley; Sidi Said, Mohand; Feczko, Joe; Flapan, Valerie; Gavigan, Michael; Ghilezan, Irene; Helgans, David; Jensen, Dennis M.; Mallen, Sharon; McCormick, Andrew B.; Miller, Tina; Natarajan, Joseph; Oleksey, Karole M.; Putnam, Elizabeth; Richler, Marsha; Shehu, Migen; Silber, Beth Ann; Walmsley, Patricia A; Widlitz, Michael; Natalicchio, Teri
SUBJECT:	ACC Press Statement on ALLHAT
DATE:	20000328

The American College of Cardiology (ACC) issued a press statement following the ALLHAT presentation by Drs. Davis and Furberg on March 15, 2000. In this statement, they recommended that physicians "discontinue use of a widely prescribed drug, an alpha-adrenergic blocker, for the treatment of hypertension". This obviously caused much concern because that was not the message communicated in the presentation at ACC.

We have been successful in getting the ACC to agree to a clarification of this press release. The attached updated press statement released on Thursday, March 23rd states in the first paragraph, "... that physicians should carefully reassess the use of alpha blocker doxazosin (Cardura) rather than automatically discontinuing its use (for hypertension)."

This "reassessment" of Cardura's role in contrast to "discontinuing" its use in hypertension represents the current official stance of the ACC and should be emphasized to physicians who felt the switching of Cardura patients was warranted based on the previous ACC recommendation.

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

LAWRENCE D. BERNHARDT, Plaintiff, vs. PFIZER, INC., Defendant.	X : : : : : : : X	00 CIV 4042 (LMM)
ARNOLD LIEBMAN, Plaintiff, vs. PFIZER, INC., Defendant.	X : : : : : : : X	00 CIV 4379 (LMM)

AFFIDAVIT OF DR. LAWRENCE R. KRAKOFF IN SUPPORT OF PLAINTIFFS' APPLICATION FOR AN ORDER TO SHOW CAUSE

STATE OF NEW JERSEY)
: ss.:
COUNTY OF BERGEN)

Dr. Lawrence R. Krakoff, being duly sworn, deposes and says:

1. I am the Chief of Medicine at Englewood Hospital and Medical Center in Englewood, New Jersey and a Professor of Medicine at Mount Sinai School of Medicine, in New York, New York. I submit this affidavit in support of plaintiffs' request for injunctive relief.

2. My area of medical expertise is in the field of hypertension. From 1975 through 1992, I served as the Chief of the Hypertension Clinic at Mount Sinai Hospital. I have been a

member of many cardiovascular study sections of the National Heart, Lung and Blood Institute (the "NHLBI"); have served as a contributor to the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; and have worked on more than 120 original articles, editorials and book chapters devoted to hypertension and related cardiovascular disorders. My curriculum vitae is attached hereto as Exhibit A. I am not involved with the ALLHAT study (described below) as an investigator, member of any committee or any other capacity.

3. I am familiar with the drug Cardura and the results of the NHLBI's Antihypertensive Lipid Lowering to Prevent Heart Attack Trial ("ALLHAT") study. In brief, Pfizer has developed Cardura (generic name doxazosin), an alpha$_1$ receptor antagonist with a prolonged (24 hour) duration of action, received FDA approval for marketing this drug and has advertised the drug as initial and "first line" treatment for hypertension. Past studies during the development of Cardura demonstrated efficacy (antihyptertensive effect) and low frequency of symptomatic adverse effects.

4. The ALLHAT study is the largest single clinical trial being conducted in the past or present to compare several important and widely used classes of antihypertensive drugs for their effect of cardiovascular mortality and morbidity. Cardura was one of the antihypertensive drugs chosen to be included in the ALLHAT study for contrast with other drugs. The interim results of the ALLHAT study (concerning Cardura) were published in April 2000 by the ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group and I have reviewed the publication of those results in detail. The results demonstrate that there is a twofold higher risk of requiring hospitalization for heart failure in the group of the ALLHAT study given

Cardura as compared with the group which was given chlorthalidine, a less expensive and widely used antihypertensive diuretic drug. There were also trends suggesting greater frequency of overall cardiovascular events in the group given Cardura as compared with the group given chlorthalidine.

5. Drug treatment of hypertension is effective for prevention of cardiovascular mortality (due to stroke or myocardial infraction, sudden death) and morbidity (non-fatal stroke, myocardial infraction, development of congestive heart failure). ALLHAT was specifically designed to address whether the benefit conferred by antihypertensive drug therapy is shared equally by several widely used drug classes and compared these drugs classes with large enough groups of patients to detect differences among treatments, should they be present. In my opinion, ALLHAT is a crucial study, that was well designed and highly likely to provide definitive answers to very important and previously unresolved questions that bear directly on how physicians should treat hypertension.

6. The first report of health-related outcomes provided by ALLHAT concerned Cardura and described an unexpected but highly significant difference between those groups treated with Cardura (doxazosin) and chlorthalidine, a less expensive and widely used antihypertensive diuretic drug. During the course of 3-4 years of observation, overall hospitalization for heart failure was twice as high in the Cardura group, compared to the chlorthalidine group. No such pattern appeared for the other two drugs used in the trial, lisinopril (marketed as Prinivil and Zestril), an Ace inhibitor, or amlodipine (marketed as Norvasc), a calcium channel blocker. Over the course of the study, heart failure occurred in 8.13% with Cardura and 4.45% with chlorthalidine; the difference in these rates implies that about 1 of every

27 patients treated with Cardura instead of chlorthalidine would be expected to be hospitalized for congestive heart failure. This is a highly significant adverse outcome (the higher rate for hospitalization for patients for heart failure treated with Cardura compared to chlorthalidine) and, in my opinion, requires a comprehensive and widely disseminated warning to physicians and patients to prevent unnecessary cardiovascular morbidity in the immediate future.

7. Given this adverse outcome, Cardura should no longer be prescribed as a "first line" drug to treat hypertension. For hypertensive patients when used in combination with other antihypertensive drugs (as a second or third line drug) or for other indications (prostatic hypertrophy), Cardura may be appropriate therapy. It is inappropriate to use Cardura other than as previously described and patients and physicians should be made aware of this.

8. To this date, I am unaware of any action by Pfizer to change its product label, to notify physicians (by advertising or direct contact) or to make the public aware (by direct-to-consumer notification or advertising) that use of Cardura as an antihypertensive agent is related to increased risk of congestive heart failure. Pfizer's delay or refusal to provide such notification to date may have already caused hospitalizations due to use of Cardura that might have been avoided.

9. I have reviewed the proposed notices sought by plaintiffs herein and believe that they are appropriate and necessary under the circumstances. First, direct patient notification is essential as medical practitioners cannot be expected to individually review their patient files, determine who has been prescribed Cardura for the treatment of hypertension and provide individual notice to all such persons. Second, written notice to physicians is required as all doctors treating hypertension should be aware of the crucial ALLHAT study and its implications

regarding the treatment of hypertension and a written uniform notification is the most effective means to communicate such information.

10. It is universally agreed that optimal treatment of hypertension with antihypertensive drugs should maximally prevent the complications of hypertension which are stroke and heart disease, including heart failure. Given the ALLHAT results, in my opinion, the relief sought by plaintiffs herein should be granted.

Dr. Lawrence R. Krakoff

Sworn to before me this
7th day of September 2000

Margaret R. Maher
Notary Public

MARGARET R. MAHER
NOTARY PUBLIC OF NEW JERSEY
MY COMMISSION EXPIRES OCTOBER 13, 2003
September 7, 2000

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

LAWRENCE D. BERNHARDT, Plaintiff, vs. PFIZER, INC., Defendant.	00 CIV 4042 (LMM)
ARNOLD LIEBMAN, Plaintiff, vs. PFIZER, INC., Defendant.	00 CIV 4379 (LMM)

AFFIDAVIT OF DR. CURT D. FURBERG IN SUPPORT OF PLAINTIFFS' APPLICATION FOR AN ORDER TO SHOW CAUSE

STATE OF NORTH CAROLINA)
: ss.:
COUNTY OF FORSYTH)

Dr. Curt D. Furberg, being duly sworn, deposes and says:

1. I am Professor of Public Health Sciences and also the Antihypertensive Lipid Lowering to Prevent Heart Attack Trial ("ALLHAT") Steering Committee Chairman and, at request, I submit this affidavit in support of plaintiffs' request for injunctive relief. My curriculum vitae is attached hereto as Exhibit A.

2. Attached hereto as Exhibit B is a copy of the published scientific article prepared by the ALLHAT Officers and Coordinators (including myself as Chairman) which sets forth the objective, design and interim results of the ALLHAT study.

3. The ALLHAT study is the largest single clinical trial being conducted in the past or present to compare several important and widely used classes of antihypertensive drugs for their preventive effect of cardiovascular mortality and morbidity. Cardura (generic name doxazosin) was one of the four antihypertensive drugs chosen to be included in the ALLHAT study for contrast with other drugs. The interim results of the ALLHAT study (concerning Cardura) are set forth in Exhibit B. The results demonstrate that there is a twofold higher risk of new, hospitalized or fatal heart failure in the group of the ALLHAT study given Cardura as compared with the group which was given chlorthalidine, a less expensive and widely used antihypertensive diuretic drug. There were also trends suggesting greater frequency of overall cardiovascular events and stroke in the group given Cardura as compared with the group given chlorthalidine.

4. Drug treatment of hypertension is effective for prevention of cardiovascular mortality (due to stroke, myocardial infarction or sudden death) and morbidity (non-fatal stroke, myocardial infarction or development of congestive heart failure). ALLHAT was specifically designed to address whether the benefit conferred by older antihypertensive drug therapy is shared equally by several widely used, newer drug classes and compared these drug classes with large enough groups of patients to detect moderate but important differences among treatments, should they be present. In my opinion, ALLHAT is a crucial study, that was well designed and

highly likely to provide definitive answers to very important and previously unresolved questions that bear directly on how physicians should treat hypertension.

5. The first report of health-related outcomes provided by ALLHAT concerned Cardura and described an unexpected but important and highly significant difference between those groups treated with Cardura (doxazosin) and chlorthalidine, a less expensive and widely used antihypertensive diuretic drug. During the course of 3-4 years of observation, overall new, hospitalized and fatal heart failure was twice as high in the Cardura group, compared to the chlorthalidine group. Over the course of the study, heart failure occurred in 8.13% with Cardura and 4.45% with chlorthalidine; the difference in these rates implies that about 1 of every 27 patients treated with Cardura instead of chlorthalidine would be expected to develop, be hospitalized or die from congestive heart failure. This is a highly unfavorable outcome (the two-fold higher risk of heart failure for patients treated with Cardura compared to chlorthalidine) and, in my opinion, merits a comprehensive and widely disseminated warning to physicians and patients to prevent unnecessary cardiovascular mortality and morbidity in the future.

6. Given this adverse outcome, Cardura should no longer be prescribed as a "first line" drug to treat hypertension. For hypertensive patients, Cardura, when used in combination with other antihypertensive drugs (as a second or third line drug) or for other indications (prostatic hypertrophy), may or may not be appropriate therapy.

7. To this date, I am unaware of any action by Pfizer to change its product label, to notify physicians (by advertising or direct contact) or to make the public aware (by direct-to-consumer notification or advertising) that use of Cardura as a first-line antihypertensive agent is related to increased risk of congestive heart failure. Pfizer's delay in providing such notification

may every year cause thousands of unnecessary cases of heart failure among the large number of hypertensive patients who currently use Cardura. I am also unaware of any action by the United States Food & Drug Administration in response to the ALLHAT findings.

8. I have reviewed the proposed notices sought by plaintiffs attached hereto as Exhibits C and D and believe that they are appropriate under the circumstances. First, written notice to physicians is required as all doctors treating hypertension should be aware of the crucial ALLHAT study and its implications regarding the treatment of hypertension and a written uniform notification may be the most effective means to communicate such information. Second, direct patient notification may be essential as medical practitioners cannot be expected to individually review their patient files, determine who has been prescribed Cardura for the treatment of hypertension and provide individual notice to all such persons. Similar notices were sent to Cardura users and administrators in the ALLHAT study. All ALLHAT patients who received Cardura in the study were taken off this medication in order to avoid excess risk of heart failure and other cardiovascular events. Pfizer agreed with this decision to terminate the Cardura arm of the ALLHAT study, given the ALLHAT findings.

9. The optimal treatment of hypertension with antihypertensive drugs should maximally prevent the major complications of hypertension which are stroke and heart disease, including heart failure. Given the ALLHAT results, in my personal opinion, the relief sought by plaintiffs herein should be granted.

Curt D. Furberg, M.D., Ph.D.
Professor of Public Health Sciences

Sworn to before me this
11th day of October 2000

Ivy C. Kiger
Notary Public

OFFICIAL SEAL
Notary Public, North Carolina
COUNTY OF FORSYTH
IVY C. KIGER
My Comm Exp 6/15/2003

EXHIBIT C - NOTICE TO PATIENTS

Dear (patient name):

You have been prescribed Cardura (doxazosin) for the treatment of hypertension. A recent study by the National Heart, Lung and Blood Institute (the "NHLBI") has demonstrated that Cardura is less effective in preventing heart failure compared to a widely used diuretic drug known as chlorthalidone. As a result, you are requested to consult with your doctor regarding your use of Cardura to treat hypertension and other possible treatment options.

DO NOT STOP TAKING YOUR CARDURA MEDICATION UNTIL YOU CONSULT WITH YOUR DOCTOR, BECAUSE THE MEDICATION MAY HELP TO KEEP YOUR BLOOD PRESSURE CONTROLLED DURING THAT TIME AND THERE MAY BE OTHER REASONS WHY YOUR DOCTOR CHOSE THIS DRUG FOR YOUR TREATMENT. After reviewing your individual circumstances, your doctor may or may not recommend that another treatment will be of more benefit to you.

EXHIBIT D - NOTICE TO PHYSICIANS

Dear (physician name):

A recent study by the National Heart, Lung and Blood Institute (the "NHLBI") has demonstrated that Cardura (doxazosin) is less effective in preventing heart failure compared to a widely used diuretic drug, chlorthalidone. This information is being provided to you as you may have prescribed Cardura for the treatment of hypertension to your patients.

The results of the study known as the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial ("ALLHAT") have been published in Volume 283, Number 15 of JAMA, on April 19, 2000. You are requested to familiarize yourself and your staff with these results, as Cardura patients are being simultaneously notified of the ALLHAT findings and instructed to contact their physicians regarding the effect of the ALLHAT study on their hypertension treatment options based on their individual circumstances.

UNITED STATES DISTRICT COURT)
: ss.: AFFIDAVIT OF SERVICE
SOUTHERN DISTRICT OF NEW YORK)

SUSAN M. GREENWOOD, being duly sworn, deposes and says:

1. I am not a party to this action, am over 18 years of age, and am associated with the firm of Milberg, Weiss, Bershad, Hynes & Lerach LLP.

2. On the 11th day of October, 2000, I caused to be served by hand the annexed PLAINTIFF'S MEMORANDUM OF LAW IN OPPOSITION TO DEFT PFIZER INC.'S MOTION FOR JUDGMENT ON THE PLEADINGS WITH RESPECT TO PLAINTIFFS' CLAIM FOR MANDATORY INJUNCTIVE RELIEF IN THE FORM OF EMERGENCY NOTICE; PLAINTIFFS MEMORANDUM OF LAW IN SUPPORT OF THEIR MOTION FOR CLASS CERTIFICATION; PLAINTIFFS' MOTION FOR CLASS CERTIFICATION PURSUANT TO FED. R. CIV. P. 23; NOTICE OF MOTION FOR CLASS CERTIFICATION; MOTION FOR INTERVENTION; NOTICE OF MOTION FOR INTERVENTION; AFFIDAVIT OF DOROTHY HOLZER; AFFIDAVIT OF ARNOLD LIEBMAN; AFFIDAVIT OF LAWRENCE D. BERNHARDT and AFFIDAVIT OF SALVATORE J. GRAZIANO in this action, upon the following named attorney at the address indicated:

LORI B. LESKIN
Kaye, Schler, Fierman, Hays & Handler LLP
425 Park Avenue
New York, NY 10022-3598

Susan M. Greenwood
SUSAN M. GREENWOOD

Sworn to before me this
11th day of October, 2000

Notary Public

STEVEN WATTENBERG
NOTARY PUBLIC, State of New York
No. 31-4946154
Qualified in New York County
Commission Expires Jan. 27, 2001

MILBERG WEISS BERSHAD HYNES
ONE PENN PLAZA
48th FLOOR
NEW YORK NY 10119
(212)594-5300

SHIP DATE: 02JAN01

ACTUAL WGT: 23 LBS SCALE

TO:
CUNEO LAW GROUP
317 MASSACHUSETTS AVENUE, N.E.
SUITE 300
WASHINGTON DC 20002
(202)789-3960

4804 8310 9484

FedEx RELEASE# 1988963

REF: GREENWOOD 200-173

FIRST OVERNIGHT BY 8 WED.

CAD# 0072768 02JAN01

Deliver by: 03JAN01

TRK# 4804 8310 9484 Form 0201

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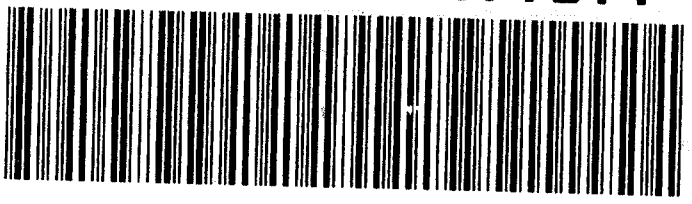

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Health and Human Services

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