CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-269

STATISTICAL REVIEW(S)

Statistical Review and Evaluation
Clinical Studies

NDA#:	21-269
APPLICANT:	Pfizer Inc.
NAME OF DRUG:	Cardura XL (Doxazosin)
INDICATION:	Treatment of Benign Prostatic Hyperplasia (BPH)
DOCUMENTS REVIEWED:	Volumes 1.1, 1.32-1.39 and SAS data dated April 20, 2001. SAS datafiles dated June 6, 2001 and August 3, 2001.

This review pertains to two studies of Cardura XL in adult males with BPH.

The medical officer for this submission is A. Batra, M.D. (HFD-580), with whom this review was discussed.

I. Background

Cardura was approved for BPH (NDA 20-371) in an IR form. It is an alpha$_1$-adrenocepter inhibitor. Alpha-blocker therapy can be associated with postural hypotension and attendant symptoms on initial dosing. Such problems are reduced by dose titration. Cardura XL is an extended release version utilizing the patented GITS (Gastrointestinal Therapeutic System) process. Doxazosin GITS is based on osmotic push technology, [redacted]

This reviewer noticed that the electronic files did not contain some information that would facilitate the review. The sponsor provided that information in their June 6, 2001 submission. This reviewer could not duplicate the sponsor's analyses exactly. Although the differences were negligible and did not affect the conclusions, this reviewer made an attempt to resolve the differences by requesting indicator random variables denoting which patients and visits were included in the primary efficacy analyses for the ITT and per protocol analyses. The sponsor provided the datasets containing the indicator random variables in their August 3, 2001 submission. These new datasets, unfortunately, did not resolve the problems. Since the differences were so minor and do not appear worthy of the effort to resolve, this reviewer will report the results in the sponsor's submission and provide the reviewer's results in brackets when the results differed.

II. Clinical Studies

A. Study Design and Method of Analyses

These were randomized, double-blind, double-dummy, multicenter trials in patients with BPH. There was a two-week screening/washout period, a two-week single blind placebo run-in period, and a 13-week double-blind treatment period. In Study DAZ-N/S/DK/95-

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Key Words: Clinical Studies, NDA Review

001, doxazosin GITS, doxazosin standard, and placebo were compared. In Study DAZ-NY-95-001, only doxazosin GITS and doxazosin standard were compared.

The total I-PSS score was obtained from seven urinary symptom questions rated over the last month on a 6-point scale (0-5 with the larger numbers being more severe) and one quality of life question on a 7-point scale (0-6 with the larger numbers indicating that the subject is feeling worse off). The maximum total I-PSS score is thus 41.

To enter the treatment phase, males aged 50-80 with symptoms of BPH had to have a total I-PSS score of greater than or equal to 12 and a maximum urinary flow rate of 5-15 ml/sec in a voided volume of greater than or equal to 150 ml during the second week of the run-in period and a weekly compliance (by tablet count) between 80 to 120%.

I-PSS total score and urinary flow rates were obtained at weeks 0, 2 (end of baseline period), 5, 9 and 15.

The subjects on doxazosin standard took 1 mg during the first week and 2 mg during the next 2 weeks. At the end of the third week of treatment (week 5 of the study), the dosage would be up-titrated to 4 mg if an adequate response was not observed. An adequate response was defined as having both: 1) An increase in the maximal flow rate of at least 3 ml/sec and 2) a reduction of the patient's total I-PSS score of at least 30% from baseline. The protocol stated that the investigator's assessment of overall improvement in BPH and changes in objective parameters should also be taken into account. The doxazosin GITS patients started at 4 mg and were kept at this dose until week 9 (dummy placebo standard were up-titrated if the patient wasn't adequately controlled to blind the dosing). At week 9 of the study, both doxazosin standard and doxazosin GITS were up-titrated to 8 mg unless the patient had an adequate response. Double-dummy techniques blinded the study even with up-titration.

The sponsor analyzed changes from baseline at endpoint for total I-PSS score and maximal urinary flow rate with an analysis of covariance including treatment and country effects with baseline as covariate. [The protocols stated that a center effect rather than a country effect would be included. The protocols also stated that treatment by center interaction would be included.]

The sponsor chose sample size with comparability of the doxazosin groups in mind. The protocols stated that 285 patients per group would be needed to achieve an 80% power with a 5% significance level. The sponsor stated that from the literature, it was estimated a standard error (SE) of 4.26 units on individual changes in scores, and using an average effect size of 1 SE of change. [This reviewer replicated the sponsor's sample size calculation assuming a delta of 1 unit and a standard deviation not SE of 4.26. These are standard sample size calculations for superiority testing not equivalence sample size calculations.]

For Study DAZ-N/S/DK/95-001, the review will focus on the ITT population because the comparison of doxazosin GITS versus placebo is the comparison of primary interest. For

consistency the ITT population of Study DAZ-NY-95-001 will also be used, even though there is no placebo treatment group in that study. Although the sponsor considered the per-protocol population to be primary because their primary focus was on the equivalence of the two doxazosin products, this review will focus on the ITT population and discuss only the general comparability of the two products.

The randomization scheme in Study DAZ-N/S/DK/95-001 was 2:2:1 with placebo having the lower rate. The randomization scheme in Study DAZ-NY-95-001 was 1:1.

The sponsor defined statistical equivalence in their statistical report, but not in their protocols, for total I-PSS score as a 95% confidence limit of the difference in mean changes from baseline completely contained in the interval (–1,1).

B. Results

1. Study DAZ-N/S/DK/95-001

There were 795 subjects (317 doxazosin GITS, 322 doxazosin standard, and 156 placebo) randomized into the study at 98 centers (20 in Denmark, 54 in Norway, and 24 in Sweden). Of these 795 subjects, 727 [295 doxazosin GITS (93.1%), 284 doxazosin standard (88.2%), and 148 placebo (94.9%)] completed the study.

The treatment groups were comparable at baseline in demographic variables.

Six subjects in the doxazosin GITS group, four subjects in doxazosin standard group and one subject in the placebo group were excluded from the ITT analyses of total I-PSS score and maximal urinary flow because they had no on-treatment values. An additional six subjects (1 doxazosin GITS, 2 doxazosin standard, and 3 placebo) were excluded from the ITT analysis of total I-PSS score because they had no baseline values.) An additional 11 subjects (7 doxazosin GITS , 3 doxazosin standard, and 1 placebo) were excluded from the ITT maximal urinary flow rate analysis because they had no on-treatment maximum urinary flow rate measurements or their voiding was interrupted.

The table below provides the final doses of the subjects in the ITT population in this study.

Final Dose (mg/Day)	Doxazosin GITS	Doxazosin Standard	Placebo
	N (%)	N (%)	N (%)
0	NA	NA	155 (100)
2	NA	37 (11.6)	NA
4	127 (40.8)	100 (31.4)	NA
8	184 (59.2)	181 (56.9)	NA
Total	311 (100)	318 (100)	155 (100)

NA Not applicable

The table below presents the results of the analysis of changes from baseline in total I-PSS score at endpoint. Both doxazosin GITS and doxazosin standard were significantly different from placebo.

Total I-PSS Score and Changes from Baseline (± Standard Deviation) in ITT Analysis Population. Reviewer's results when different are given in brackets.

	Doxazosin GITS	Doxazosin Standard	Placebo	p-VALUE
N	310	316	152	
Total I-PSS at Baseline	17.74 ± 4.31	17.78 ± 4.48	17.95 ± 4.31	0.783[a]
Total I-PSS at End of Study	9.71 ± 5.34	9.31 ± 5.30 [9.30±5.31]	11.78 ± 5.49 [11.80±5.49]	
Change from baseline	-8.02 ± 5.35 [-8.03±5.35]	-8.47 ± 5.49 [-8.48±5.48]	-6.17 ± 5.17 [-6.14±5.15]	
Change LSMean	-8.01 ± 0.30[b] [-8.02 ± 0.30[b]]	-8.45 ± 0.29[b] [-8.46 ± 0.29[b]]	-6.06 ± 0.41[b] [-6.04 ± 0.41[b]]	<0.001
P-value vs Placebo	<0.001	<0.001		

[a] Using Kruskal-Wallis test.
[b] Standard error rather than standard deviation.

The 95% confidence limit on the differences of LSMEAN changes from baseline for doxazosin GITS-doxazosin standard is (-0.32, 1.21). This fails the sponsor's definition of statistical equivalence.

The table below provides the results of the analysis of changes from baseline in maximal urinary flow rate at endpoint for the ITT population. Both doxazosin GITS and doxazosin standard were significantly different from placebo.

Changes from Baseline in Maximal Urinary Flow Rate (ml) at Endpoint (± Standard Deviation) in ITT Analysis Population. Reviewer's results when different are given in brackets.

	Doxazosin GITS	Doxazosin Standard	Placebo	p-VALUE
N	304	315	154	
Baseline MUFR	10.30 ± 2.63	9.98 ± 2.77	9.86 ± 2.63	0.215[a]
MUFR at End of Study	12.88 ± 4.54 [12.87±4.55]	12.26 ± 4.41	10.94 ± 3.95 [10.87±3.86]	
Change from baseline	2.58 ± 4.12 [2.57±4.13]	2.27 ± 3.74	1.07 ± 3.83 [1.01±3.67]	
Change LSMean	2.63 ± 0.24[b]	2.24 ± 0.23[b]	1.02 ± 0.32[b] [0.96±0.32[b]]	<0.001
P-value vs Placebo	<0.001	0.001		

[a] Using Kruskal-Wallis test.
[b] Standard error rather than standard deviation.

The 95% Confidence limit on the differences of LSMEAN changes from baseline for Doxazosin GITS-Doxazosin standard is (-0.22, 1.00).

2. Study DAZ-NY-95-001

There were 680 subjects (350 doxazosin GITS and 330 doxazosin standard) randomized into the study at 69 centers (7 in Germany, 8 in Poland, 11 in Canada, 10 in the United Kingdom, 6 in Hungary, 7 in Belgium, 12 in the Republic of South Africa, 4 in Ireland, and 4 in Italy). Of these 680 subjects, 610 [311 doxazosin GITS (88.9%) and 299 doxazosin standard (90.62%)] completed the study.

Ten subjects in the doxazosin GITS group and eight subjects in doxazosin standard group were excluded from the ITT analyses of total I-PSS score and maximal urinary flow because they had no on-treatment values. An additional seven subjects (five doxazosin GITS and two doxazosin standard) were excluded from the ITT analysis of total I-PSS score because they had no baseline values.) An additional six subjects (three doxazosin GITS and three doxazosin standard) were excluded from the ITT maximal urinary flow rate analysis because they had no on-treatment maximum urinary flow rate measurements, no baseline measure, comment for maximal flow measurement indicated a false peak, or their voiding was interrupted.

The treatment groups were comparable at baseline in demographic variables.

The table below provides the final doses of the subjects in the ITT population in this study.

Final Dose (mg/Day)	Doxazosin GITS	Doxazosin Standard
	N (%)	N (%)
2	NA	38 (11.8)
4	145 (42.6)	92 (28.6)
8	195 (57.4)	192 (59.6)
Total	340 (100)	322 (100)

NA Not applicable

The table below presents the results of the analysis of changes from baseline in total I-PSS score at endpoint. The doxazosin GITS and doxazosin standard groups were not significantly different.

Total I-PSS Score and Changes from Baseline (± Standard Deviation) in ITT Analysis Population. Reviewer's results when different are given in brackets.

	Doxazosin GITS	Doxazosin Standard	p-VALUE
N	335	320	
Baseline Total I-PSS	18.37 ± 5.00	18.33 ± 4.84	0.804[a]
Total I-PSS at End of Study	10.35 ± 5.73 [10.28±5.73]	10.58 ± 5.58 [10.53±5.58]	
Change from baseline	-8.02 ± 5.57 [-8.08 ± 5.54]	-7.75 ± 5.45 [-7.80 ± 5.46]	
Change LSMean	-8.00 ± 0.30[b] [-8.07 ± 0.30[b]]	-7.78 ± 0.30[b] [-7.83 ± 0.30[b]]	0.553 [0.534]

[a] Using Wilcoxon rank sum test.
[b] Standard error rather than standard deviation.

The 95% confidence limit on the differences of LSMEAN changes from baseline for Doxazosin GITS-Doxazosin standard is (-0.98,0.53). This just meets the sponsor's definition of statistical equivalence.

The table below provides the results of the analysis of changes from baseline in maximal urinary flow rate at endpoint for the ITT population. The doxazosin GITS and doxazosin standard groups were not significantly different.

Changes from baseline in Maximal Urinary Flow Rate (ml) (± Standard Deviation) in ITT Analysis Population

	Doxazosin GITS	Doxazosin Standard	p-VALUE
N	337 [336]	319 [318]	
Baseline MUFR	10.46 ± 2.89	10.53 ± 2.64	0.793[a] [0.818]
MUFR at End of Study	13.02 ± 4.61	12.95 ± 4.95 [12.95 ± 4.96]	
Change from baseline	2.57 ± 4.27 [2.56 ± 4.27]	2.42 ± 4.61	
Change LSMean	2.74 ± 0.26[b] [2.73 ± 0.26[b]]	2.61 ± 0.27[b]	0.705 [0.718]

[a] Using Wilcoxon rank sum test.
[b] Standard error rather than standard deviation.

The 95% confidence limit on the differences of LSMEAN changes from baseline for Doxazosin GITS-Doxazosin standard is (-0.54,0.80).

C. Reviewer's Comments

This reviewer was not able to replicate the sponsor's results exactly with datafiles provided on April 20, June 6, and August 3, 2001. The differences were so minor that they are not worth the additional effort to resolve. [In some of the analyses there were minimal differences in the means and least squares means.] These differences would not affect the conclusions of the review.

Study DAZ—N/S/DK/95-001 showed both doxazosin treatments to be superior to placebo for changes from baseline in endpoint total I-PSS score and endpoint maximal urinary flow rate.

Since these studies used titration to final dose with starting doses different, formal testing of equivalence is somewhat problematic as is the sponsor's definition of equivalence. The doxazosin standard group can stop at 2 mg whereas the doxasosin GITS group can not stop at 2 mg. About 11.7% of doxazosin standard subjects stopped at this dose. Since the two studies differed in which treatment gave better results for total I-PSS score (doxazosin GITS was better in both studies for maximal urinary flow rate) and were of comparable size for the active treatments, the two doxazosin treatments can be said to give comparable results.

Since there are a large number of small centers it is appropriate not to include treatment-by-center interaction and use country rather than centers as a factor.

III. Overall Comments

Study DAZ—N/S/DK/95-001 showed both doxazosin treatments to be superior to placebo for changes from baseline in endpoint total I-PSS score and endpoint maximal urinary flow rate. Since the two studies differed in which treatment gave better results for total I-PSS score and were of comparable size for the active treatments, the two doxazosin treatments can be said to give comparable results. Doxazosin GITS gave slightly more reduction in maximum urinary flow rate in both studies.

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Concur: Dr. Welch

This review contains 8 pages of text.
cc:
Archival NDA 21-269
HFD-580

HFD-580/Dr. Batra
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HFD-715/Dr. Gebert
HFD-715/Dr. Nevius
HFD-715/Dr. Welch

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Mike Welch
10/29/01 11:33:51 AM
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Concur with review

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11/2/01 10:16:42 AM
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