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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-287

Statistical Review(s)

STATISTICAL REVIEW AND EVALUATION

NDA:	21-287
Trade Name:	Uroxatral
Generic Name:	Alfuzosin Hydrochloride
Applicant:	Sanofi-Synthelabo Inc.
Indication:	Treatment of the signs and symptoms of Benign Prostatic Hperplasia.
Date of Submission:	December 8, 2000
Project Manager:	Evelyn Farinas, HFD-580
Clinical Reviewer:	George Benson, MD, HFD-580
Statistical Reviewer:	Mahboob Sobhan, Ph.D., HFD-715

Summary: The sponsor, Sanofi-Synthelabo Inc., seeks approval of Uroxatral 10 mg once a day (OD) extended release formulation, for the treatment of signs and symptoms of benign prostatic hyperplasia (BPH). Currently, Uroxatral 2.5 mg three times a day (TID) immediate-release and 5 mg twice a day (BID) sustained-release formulations are marketed in Europe. The sponsor claims that Uroxatral 10 mg OD formulation is bioequivalent to Uroxatral 2.5 mg TID. To support this new formulation, the sponsor conducted three placebo-controlled, double-blind, randomized, multicenter trials (one in the US and two in Europe) in patients with symptomatic Benign Prostatic Hyperplasia (BPH). Following 28 days of placebo run-in period, patients were randomized to receive either Uroxatral or placebo and followed up at days 28, 56, and 84 for safety and efficacy assessment. The objectives of these trials were to compare the safety and efficacy of Uroxatral 10 mg OD formulation to placebo. Efficacy was assessed by the improvements (change from day 0 to day 84) in International Prostate Symptom Score (IPSS), Peak Flow Rate (PFR), quality of life (QOL), patients well-being and perceived sexual life (measured by Urolife scale), and clinical global impression (CGI) that measured both efficacy and safety. Of these, IPSS and PFR were considered the primary efficacy outcome. The studies were designed with adequate number of patients to detect the differences in improvement in IPSS and PFR between the Uroxatral and placebo dose groups. The demographic and baseline characteristics of Uroxatral and placebo patients were similar across treatment groups and studies. The results from all three trials demonstrated significantly ($p < .01$) higher improvement in prostate symptom score (IPSS) and peak flow rate (PFR) for Uroxatral 10 mg OD dose group compared to placebo. The improvement in the Quality of life outcome, perceived well-being and sexual life has also been noted for Uroxatral therapy, although the results were statistically significant only in the US study and trended in the positive direction in the European trials. Overall, adjusting for multiple dose comparisons and multiple endpoints, the sponsor's result demonstrated superiority of Uroxatral 10 mg OD formulation over placebo in the improvement of prostate symptom scores and flow rate.

Keywords: Clinical studies; NDA review

Table of Contents

1.0 INTRODUCTION

1.1 Background

Uroxatral (Alfuzosin HCL) was developed and marketed in Europe for the treatment of benign prostatic hyperplasia (BPH). Two formulations of Uroxatral are currently marketed in Europe: an immediate-release formulation, administered as 2.5 mg three times a day (TID) and a sustained-release formulation, administered as 5 mg twice daily (BID). In this application, the sponsor seeks approval for a prolonged-release formulation of Uroxatral 10 mg once daily (OD), in the hope that the new formulation would improve compliance and lower incidence of adverse events. They also claim that the bioequvalence between the new formulation and Uroxatral 2.5 mg TID has been demonstrated in healthy volunteers.

To support Uroxatral 10 mg extended-release (ER) regimen, the sponsor conducted four safety and efficacy studies with doses 2.5 mg TID, 10 mg OD, and 15 mg OD of Uroxatral formulation compared to placebo.

This review will address the efficacy outcome pertaining to Uroxatral 10 mg dose only and, therefore, three trials that included Uroxatral 10 mg dose arm will be reviewed in the following sections. Safety evaluation can be found in Medical officer's review.

1.2 Indication

The sponsor's proposed indication for Uroxatral:

> "*Uroxatral is indicated for the treatment of the signs and symptoms of benign prostate hyperplasia*".

1.3 Summary of Controlled Studies

To support the safety and efficacy of new formulation of Uroxatral, the sponsor conducted four placebo-controlled trials with a dose ranging from 2.5 to 15 mg of Uroxatral. But only three placebo-control trials had a 10 mg dose arm. Of these, two studies were conducted in Europe (ALFORTI and ALFOTAM) and one study was conducted in the US (ALFUS). The main study features are summarized in Table 1.

Table 1 Summary of Phase III Pivotal Studies			
Study Name (Location) (Report #)	Study Design	Treatment (Number of subjects)	Objective(s)
ALFORTI (Europe) (98-00741)	Placebo-controlled, randomized, multicenter with: • 4-week single-blind placebo run-in period followed by • 12-week double-blind Phase.	Uroxatral 2.5 mg TID (150) Uroxatral 10 mg OD (143) Placebo (154)	• Compare the safety and efficacy of Uroxatral 10 mg OD and Uroxatral 2.5 mg TID (marketed European formulation) vs. placebo.
ALFORTAM (Europe) (99-00925)	Placebo-controlled, randomized, multicenter with: • 4-week single-blind placebo run-in period. • 12-week double-blind Phase.	Uroxatral 10 mg OD (154) Uroxatral 15 mg OD (159) Tamsulosin 0.4 mg OD (158) Placebo (154)	• Compare the safety and efficacy of Uroxatral 10 mg and 15 mg OD vs. Tamsulosin 0.4 mg OD and placebo.
ALFUS (USA) (99-00591)	Placebo-controlled, randomized, multicenter with: • 4-week single-blind placebo run-in period. • 12-week double-blind Phase.	Uroxatral 10 mg OD (177) Uroxatral 15 mg OD (181) Placebo (178)	• Compare the safety and efficacy of Uroxatral 10 mg and 15 mg OD dose vs. placebo.
IPSS: International Prostate Symptom Score; QOL: Quality of Life; HRQL: Health-Related Quality of life Scale.			

1.4 Review Issues

In reviewing the study protocols, this reviewer finds the following design issues that may have implicated the study findings:

(1) Lack of clinical justification of the effect size, i.e., hypothesized difference (3 points on subjectively assessed score) in primary endpoint between placebo and test dose.

(2) Failure to measure compliance,

(3) Center dependency, i.e., same study centers participated in both European trials,

(4) Statistical adjustment for the multiple endpoints (two endpoints were considered primary) and multiple comparisons (several dose groups comparison) since the goal was to test a single hypothesis for the 10 mg OD group vs. placebo.

As stated in the introduction, one of the sponsor's goal was to achieve better compliance and lower incidence of adverse events with the prolonged-release formulation. The original

protocol planned to measure compliance by counting the percentages of total number of tablets taken by the patient. A compliance with treatment of less than 80% was considered to be a major protocol violation. But in an amendment, the sponsor decided not to measure compliance and the reason for such change was not justified in the study report. In the clinical trial, specifically in patient administered treatment plan, compliance would have been an important predictor of efficacy.

Regarding issue (3) and (4), the sponsor conducted statistical analysis that adjusted for center dependency and multiple comparisons. Due to large number of centers, instead of considering individual center as a factor, they considered country as a factor. This review will focus on the sponsor's efficacy analysis and verify the results with respect to (3) and (4) above. In addition, we will compare the results between Intent-to-treat analysis using the last observation carried forward (LOCF) method for missing values and the evaluable (completer's as defined by the sponsor) analysis.

2.0 EFFICACY EVALUATIONS

Details of the study design, conduct and the pertinent efficacy results are evaluated and discussed in the following sections.

2.1 Study Descriptions

2.1.1 Objective

The main objectives of all three Phase III trials were to compare the safety and efficacy of Uroxatral 10 mg once a day extended release formulation compared to placebo. In addition, the secondary objectives of the European protocols were to compare the efficacy of currently marketed formulation of Uroxatral 2.5 TID in Europe to that of 10 mg OD formulation. They didn't clarify the role of Tamsulosin 0.4 mg OD arm in one of the European trial.

2.1.2 Design

These were randomized, double-blind, multicenter, parallel group trials consisting of a 28-day single-blind placebo run-in period (Phase A) followed by an 84-day double-blind treatment period (Phase B). The basic designs were similar across trials except the differences in the dosage. Both European trials included currently marketed Uroxatral 2.5 mg TID and Tamsulosin 0.4 OD arm in addition to Uroxatral 10 mg and 15 mg OD dose arm. In phase A, all patients received the placebo and in phase B, patients received either test drug (Uroxatral or tamsulosin) or placebo. Six visits were scheduled during phases A and B: a screening visit on day 28 of the run-in period, a baseline visit on day 0 and follow-up visits on day 14, 28, 56, and 84 of the treatment Phase.

Patients were considered eligible if they were aged ≥ 50 years old; had symptomatic BPH with international prostate symptom score (IPSS) of ≥13 at day 28 and had peak flow rate (PFR) between 5 and 12 mL/s.

2.1.3 Efficacy Parameters

The primary efficacy variables were as follows:

(i) *Improvement (change from day 0 to day 84) in IPSS score* (International Prostate Symptom Score) where IPSS was self assessed by the patient based on a 5 point scale on each of 7 questions;

(ii) *Improvement in Peak Flow Rate (PFR)* - objectively measured by Uroflowmetry.

The secondary efficacy variables were:

(i) Improvement in quality of life (QOL) index,

(ii) Improvement in Urolife Scale (measures patients well-being, perceived sexual life and BPH-specific interference),

(iii) Global Subjective Assessment (GSA),

(iv) Clinical Global Impression Scale (CGI) which measures both the efficacy and adverse events, and

(v) Reduction in residual urine.

(vi) Prostate Volume

2.1.4 Study Hypothe ses

The trials were sized to reject the null hypothesis that there were no differences in change from baseline to endpoint in IPSS and PFR between Uroxatral dose groups and Placebo.

2.1.5 Sample size

To reject the above null hypothesis, the sponsor estimated the sample sizes according to the assumed effect sizes as shown in Table 2.

Table 2
Sample Sizes by Study

Study	Effect size: Differences (Uroxatral vs. placebo)	Power	Treatment groups	Number of patients (Randomized)
ALFOTAM	2.9	80%	4	625
ALFORTI	2.5	80%	3	447
ALFUS	2.9	80%	3	536

2.1.6 Statistical Methods

The statistical methods employed were: analysis of variance (ANOVA) which was primary for the treatment difference without any adjustment for baseline values and analysis of

covariance (ANCOVA) with an adjustment for baseline values; and Cochran-Mantel-Haenszel (CMH) chi-square test for the qualitative (categorized) parameters. The protocols planned to analyze three populations: ITT (intent-to-treat), PP (per protocol) and Completers. The ITT was defined as all randomized patients who received at least one dose of study drug, had one baseline and one post-drug evaluation of the two primary efficacy variables. The PP population composed of patients who met the ITT definition, had fewer than 2 visits with major protocol violations and the Completers were composed of patients who met the ITT definition and who also completed the study for 84 ±14 days. Country and country by treatment interaction effect was also included in the ANOVA model. Adjustment for multiple comparisons was made by Dunnett method for quantitative variables and by Bonferroni-Holm procedure for qualitative variables.

2.1.7 Reviewer's comment

The sample sizes were adequate to reject the null hypothesis that the improvement in IPSS do not differ between Uroxatral and placebo group. However, the clinical implications of the effect sizes of <=3 points (where IPSS ranges from 3-35) assumed to design these studies were less clear.

2.2 Results

2.2.1 Patient Disposition

There were 47 (7%), 40 (9%), and 72 (13%) patients, in ALFOTAM, ALFORTI and ALFUS respectively, who discontinued the trials prematurely. The most frequent reason of discontinuation was adverse event (generally low and similar in both treatment groups), more in Uroxatral dose groups than placebo. In general, however, the discontinuation rate was similar across studies and treatment groups.

Table 3 depicts the number of ITT and 'completers' population for placebo and Uroxatral 10 mg OD dose group only. For ITT analysis, LOCF method was used to impute the missing data at endpoint while no imputation method was used for the analysis of 'completers' population.

Table 3
Disposition of Analysis Population

Study	Analysis population	Placebo	Uroxatral 10 mg OD
ALFOTAM	Exposed	153	154
	ITT	150	151
	Completers	140	138
ALFORTI	Exposed	154	143
	ITT	152	137
	Completers	141	128
ALFUS	Exposed	175	176
	ITT	167	170
	Completers	160	153

2.2.2 Baseline characteristics

Demographic and baseline characteristics were generally well balanced between treatment groups across studies. The mean age of the study population was 64 years and the majority of the patients were caucasians (97-100% in Europe and 90% in the US). The baseline IPSS score was higher in the US study than European studies (approximately 21 in the US, and 17 and 20 in the European studies) while peak urinary flow rate was similar across studies.

2.2.3 Primary Efficacy

The primary efficacy endpoints were the mean change in the total symptom score (IPPS) and peak flow rate (PFR) from baseline to day 84 of the double-blind treatment phase. The efficacy analysis goal was to compare the differences in mean change between Uroxatral 10 mg and placebo group. Results of the ITT population analysis for the two groups are shown in Table 4. At endpoint, the improvement (reduction in symptom score) in total symptom score was statistically significantly ($p<.01$, adjusting for two group comparison) higher for Uroxatral 10 mg OD group compared to placebo group across all studies. On an average, symptom score improved by 2.0 points in all three studies. Similarly, improvement (increase in flow rate) in the peak flow rate (PFR) was also statistically significantly ($p<.05$) higher for Uroxatral group in 2/3 studies. For patients in ALFOTAM trial, the improvement trended in the same direction, although not significant ($p>.05$). Results at earlier time points, i.e., at day 28 and 56 of the double-blind phase (not shown here), consistently demonstrated the superiority of Uroxatral compared to placebo. No significant center or center by treatment effect was noted in these studies. The sponsor's efficacy analyses demonstrate that Uroxatral 10 mg once a day extended release formulation is superior to placebo in reducing prostate symptom score and improve flow rate in symptomatic BPH patient. It is important to note that during run-in phase in the US trial, when each patient received a placebo pill the IPSS score improved by even a greater amount (average of 3 points), though equally in both placebo and Uroxatral group. Similar observation was not noted in the European trials.

Table 4
Primary Efficacy by Study (ITT Population)

Endpoints:	ALFUS Protocol (US)		ALFORTI Protocol (EUROPE)		ALFOTAM Protocol (EUROPE)	
	Placebo (n=167)	Uroxatral 10 mg (n=170)	Placebo (n=152)	Uroxatral 10 mg (n=137)	Placebo (n=150)	Uroxatral 10 mg (n=151)
Symptom Score(IPSS)						
Baseline	18.2	18.2	17.7	17.3	17.7	18.0
Change	-1.6	-3.6	-4.9	-6.9	-4.6	-6.5
P-value+	--	0.001	--	0.002	--	0.007
Peak flow Rate (PFR)						
Baseline	10.2	9.9	9.2	9.4	9.3	9.5
Change	0.2	1.7	1.4	2.3	0.9	1.5
p-value+	--	0.0004	--	0.03	--	NS**

* Adjusted for two pairwise comparisons.
** P>0.05

2.2.4 Secondary Efficacy

In addition to secondary variables listed in A3, the sponsor also performed secondary analysis by arbitrarily grouping (what they considered clinically meaningful improvement by a specified amount) the primary endpoints. Table 5 shows the results of the secondary analyses performed on primary as well as secondary variables.

Improvement (>=3) in symptom score (IPSS) was significantly ($p<.03$) higher in Uroxatral 10 mg OD dose group compared to placebo group across all studies. This is not surprising since the null hypothesis was rejected in the primary analysis. However, the relative improvement of 50% or more was not significantly higher for test dose group compared to placebo group in 2 out of 3 studies. Similar conclusions could be made for peak flow rate (PFR). In general, arbitrary grouping is prone to potential misclassification bias and the results from such analysis are less robust.

Quality of life (QOL) scores improved significantly for Uroxatral patients compared to placebo patients in 2/3 studies. However, patient well-being and perceived sexual life (measured by Urolife scale) was not statistically significantly different between Uroxatral and placebo patients in 2/3 studies. Both QOL and Urolife measures were significantly improved for Uroxatral patients in the US but less pronounced for European patients. This could be due to cultural differences in the way the subjective assessment of such perceived notions of self well-being are assessed in Europe compared to US.

Global satisfaction score and prostate volumes were not evaluated in the European trial, nevertheless, no significant differences between the test and placebo were noted for the above outcomes in the US study.

2.2.5 Comments on Efficacy Results

Results of ITT population analysis demonstrates that improvement in signs and symptoms (IPSS and PFR) of BPH was statistically significant for Uroxatral 10 mg OD compared to placebo. There was no significant center (country effect) or center by treatment interaction effect on the overall reults. Adjusting for two group comparisons, the results were consistently superior for Uroxatral compared to placebo. Quality of life was also improved after Uroxatral therapy but other secondary endpoints were not consistently superior for Uroxatral across all studies, though there was positive trend in favor of Test drug compared to placebo.

Results for 'completers' population were also consistently similar to ITT analysis.

Table 5
Secondary Efficacy Endpoints by Study (ITT Population)

Secondary Endpoints:	ALFUS		ALFORTI		ALFOTAM	
	Placebo (n=167)	Uroxatral 10 mg (n=170)	Placebo (n=152)	Uroxatral 10 mg (n=137)	Placebo (n=150)	Uroxatral 10 mg (n=151)
Symptom Score (IPSS)						
Absolute improvement:						
<3	102(61%)	75(44%)	49(32%)	26(19%)	54(36%)	29(19%)
>=3	65(39%)	95(56%)	103(68%)	111(81%)	96(64%)	122(81%)
P-value+	--	<.005	--	0.02	--	0.002
Relative improvement:						
<50%	151(90%)	146(86%)	113(74%)	86(63%)	115(77%)	101(67%)
>=50%	16(10%)	24(14%)	39(26%)	51(37%)	35(23%)	50(33%)
P-value+	--	NS	--	0.006	--	NS
Peak Flow Rate (PFR)						
Absolute improvement:						
<2 ml/s	124(74%)	102(60%)	96(65%)	70(51%)	103(69%)	88(58%)
>=2 ml/s	43(26%)	68(40%)	51(35%)	66(49%)	47(31%)	63(42%)
p-value+	--	0.008	--	0.02	--	NS
Relative Improvement:						
<30%	132(79%)	113(66%)	104(71%)	85(62%)	110(73%)	94(62%)
>=30%	35(21%)	57(34%)	43(29%)	51(38%)	40(27%)	57(38%)
p-value+	--	0.02	--	NS	--	NS
Quality of Life (QOL):						
Baseline	3.7	3.8	3.3	3.3	3.6	3.5
Change	-0.3	-0.7	-0.6	-1.1	-1.0	-1.0
p-value+	--	0.002	--	<.002	--	NS
Urolife Total Score:						
Baseline	48.8	45.5	49.0	51.4	50.2	50.0
Change	-1.3	1.9	1.8	4.0	0.9	3.3
p-value+	--	0.01	--	NS	--	NS
Global Satisfaction (BSF) subscore:						
Baseline	2.0	1.9	--	--	--	--
Change	0.0	-0.1	--	--	--	--
p-value+	--	NS	--	--	--	--
Prostate Volume (ml):						
Baseline	36.6	40.4	--	--	--	--
Change	1.0	-1.3				
p-value+	--	NS	--	--	--	--

+ Adjusted for two pairwise comparisons.

3.0 REVIEWER'S ASSESSMENT AND RECOMMENDATIONS

This review evaluated the efficacy results of the studies conducted in the US and Europe in support of Uroxatral 10 mg once a day prolonged-release formulation compared to placebo, in the treatment of signs and symptoms of benign prostatic hyperplasia (BPH). Our assessment is based on the strength and weaknesses of the study design employed, statistical evidence shown and its implication on the indication sought in this application.

Three placebo-controlled, randomized, multicenter trials with identical but independent protocols were conducted in symptomatic BPH patients. Presuming valid effect sizes, all studies were powered with adequate number of patients.

The effect size issue was discussed with the clinical reviewer who clarified that the improvement in average symptom score by an average of 3 points was an acceptable amount to design BPH studies. We also pointed out that there was strong placebo effect in the US study during the single blind run-in phase, where the average symptom score improved by 3 points from baseline and continued to the end of the double-blind phase. However, the placebo effect was similar in both Uroxatral and placebo group. As per statistical adjustment of center effect and multiple comparison, the sponsor performed appropriate analysis to account for such adjustment. This reviewer independently verified the efficacy outcome using the data provided by the sponsor in this submission and finds that the results are similar for both ITT and 'completers' population. Based on the results submitted, we can conclude that:

(1) Uroxatral 10 mg once daily prolonged-released formulation was statistically significantly ($p<.01$, adjusting for multiple comparison) superior to placebo in improving the prostate signs and symptoms (IPSS and PFR) in BPH patients.

(2) Uroxatral therapy also improved the Quality of life outcome, perceived well-being and sexual life, although the results were statistically significant only in the US study and trended in the positive direction in the European trials.

From statistical perspective, this reviewer concludes that the efficacy results submitted in this application demonstrate evidence in support of Uroxatral 10 mg OD in the treatment of signs and symptoms of BPH.

/S/

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