

NONPRESCRIPTION DRUGS  
ADVISORY COMMITTEE AND  
ARTHRITIS ADVISORY  
COMMITTEE

JULY 20, 1999

NDA 21070 FLEXERIL OTC  
SWITCH

STATISTICAL SUMMARY

ADDENDUM TO:

NDA 21-070 Statistical Summary

Flexeril<sup>MR</sup> (cyclobenzaprine hydrochloride) Nonprescription 5 mg tablets

On page 2 of the Statistical Summary, the final sentence of the paragraph concerning the Label Comprehension Study should be deleted.

 7/19/99

Lillian Patrician, MS, MBA  
Mathematical Statistician

Concur:  7/19/99       Dr. Mohammad Huque      Dr. Stan Lin

cc:            Orig. NDA 21-070  
                 HFD-550/File  
                 HFD-550/DeLap/Hyde/Witter/Schmidt  
                 HFD-560/Ganley/Katz/Neuner/Rothschild  
                 HFD-120/Laughren/Andreason  
                 HFD-725/File  
                 HFD-725/Huque/Lin/Patrician  
                 Chron.

## NDA 21-070 Statistical Summary

Flexeril<sup>MR</sup> (cyclobenzaprine hydrochloride) Nonprescription 5 mg tablets

11/11 / 3 1999

The Review of Efficacy Studies 006 and 008 evaluated the results on 3 primary parameters, which were patient assessments measured on a 5-point categorical scale. There is some uncertainty regarding independence of these 2 studies because 13 investigational centers conducted both studies and introduced the element of overlapping centers and patients. Nevertheless, the results for all 1,380 patients enrolled demonstrate that at Visit 3 (Day 7), there were statistically significant differences between Flexeril 5 mg and placebo in both studies. At Visit 2 (Day 3), statistical superiority was achieved in Study 006, but not replicated in Study 008. Even though results indicate statistical superiority compared to placebo, there may not be clinically meaningful significance. Efficacy results indicate that Flexeril treatment groups achieved at most a half-unit improvement over placebo in terms of estimated treatment means.

## Primary Efficacy Treatment Means

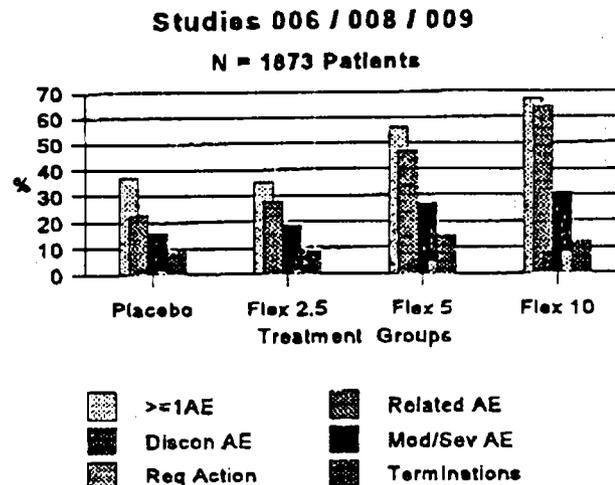
	Flex 5 mg Mean	Placebo Mean	Treatment Difference Mean	Mean Analysis
<b>Study 006</b>	<b>Day 3 / Day 7</b>	<b>Day 3 / Day 7</b>	<b>Day 3 / Day 7</b>	<b>Day 3 / Day 7</b>
Global Change	2.3 / 2.9	1.9 / 2.5	0.42 / 0.41	p<0.0001 / p<0.0001
Rating of Medication	1.6 / 2.1	1.2 / 1.7	0.45 / 0.53	p<0.0001 / p<0.0001
Diary on Relief	1.7 / 2.4	1.4 / 2.0	0.44 / 0.45	p<0.0003 / p<0.0003
<b>Study 008</b>				
Global Change	2.2 / 2.8	2.0 / 2.4	0.12 / 0.35	NS / p<0.0004
Rating of Medication	1.5 / 2.0	1.2 / 1.5	0.17 / 0.36	NS / p<0.009
Diary on Relief	1.6 / 2.2	1.3 / 1.7	0.22 / 0.42	NS / p<0.002

Global Change: 0=worsening    1=no change    2=mild    3=moderate    4=marked improvement  
 Rating of Meds: 0=poor    1=fair    2=good    3=very good    4=excellent  
 Diary of Relief: 0=none    1=little    2=some    3=lot    4=complete

The efficacy evaluation also compared the Flexeril 5 mg group to placebo by examining the distribution of patients' categorical responses per treatment group for Visit Days 3 and 7. For both studies and on both visits, the predominant pattern of distributions indicates that a numerically greater percentage of Flexeril 5 mg patients scored in the upper levels of the categorical efficacy scales, i.e. "mild, moderate, and marked improvement" in global impression of change; "good to excellent" rating of medication; and "some to complete" relief. For the highest ranking of marked improvement, excellent rating, and complete relief, there were consistent results in both studies, with few exception, in favor of Flexeril 5 mg over placebo. [Charts # 1 & 2, Pages 3-4]

Equal percentages (29%) of Flexeril and placebo patients from the 2 efficacy studies took concomitant medications that could have affected the efficacy assessments, and were disallowed by protocol: approximately 25% Flexeril and placebo patients used noninvasive therapies; 2% took other muscle relaxants; 1% took anti-inflammatory drugs; 1.5% took central nervous system drugs; and 1% took cold remedies concomitantly.

The Safety Profile of the 2 efficacy studies and 1 open-label study indicates that as compared to placebo, a higher percentage of Flexeril patients 1) discontinued due to adverse experiences; 2) reported at least 1 adverse experience; 3) reported treatment-related adverse experiences; 4) reported moderate to severe adverse experiences; and 5) reported adverse experiences requiring action to be taken. Furthermore, the percentage of Flexeril patients experiencing these adverse events increased with increasing dosage of drug. The Flexeril OTC 5 mg t.i.d. dose had a comparable safety profile to that of the prescription-strength dose, and both the 5 mg and 10 mg groups separated statistically ( $p < 0.05$ ) from placebo with regard to adverse experiences.



Because of the above dose-related adverse experiences, there may be concern regarding safety of this drug in an OTC setting in that patients who self-medicate might be inclined to repeat doses prematurely if unable to attain satisfactory relief, and the general population may hold a more relaxed concept of OTC medications than of those prescribed and under advisement of their physicians and pharmacists.

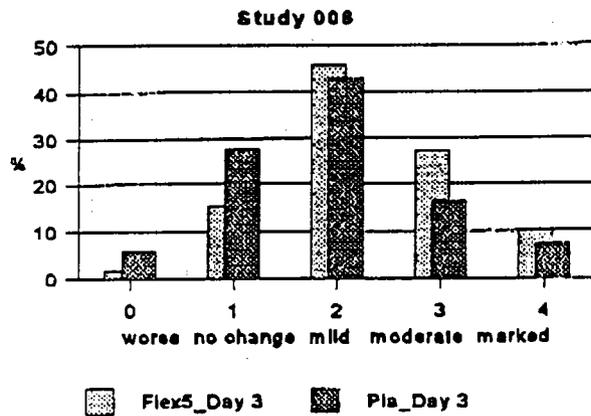
The Open-label, Pattern-of-use Study (009) indicates that the majority of patients (57%) chose to exceed the 7-day label limit by taking Flexeril 5 mg for 8 to 15 days. Rather than follow the t.i.d. dosing instruction, 8% of the patients self-medicated 4 to 6 times per day, and 13% took 20 to 30 mg per day. Eleven percent of these patients exceeded the recommended over-the-counter single dose of Flexeril 5 mg; 10% self-medicated with 2X dose equivalent to the prescription-strength 10 mg dose, and 3 patients took 15 to 20 mg per dose. Of patients with a previous history of muscle relaxant use, 14% chose to take more than the advised 15 mg per day.

The Label Comprehension Study did not take into account any possible involvement of selection bias in that administrators may have subconsciously approached those who appeared to be likely successful responders to questions. Also, the survey only questioned the public's ability to read and comprehend the product label given them. It did not address the more serious issues of how the overall population views OTC medication; of whether people consistently reread the label on OTC medication; of the likelihood that they read OTC product labels during the middle of the night or after several hours of physical distress; or what actions they typically take if the medication fails to meet their expectations of relief. Additionally, it did not address the potential of abuse in allowing a drug that affects the central nervous system to be freely available to anyone who might intentionally use this to influence the psychomotor ability of another person.

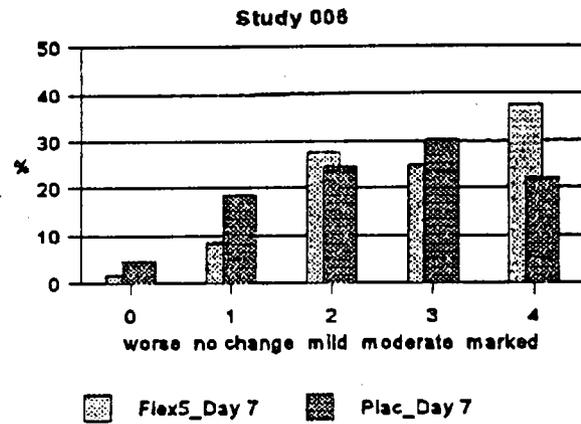
NDA 21-070 Flexeril 5 mg  
Efficacy Study 006 Distribution of Categorical Responses

Chart #1

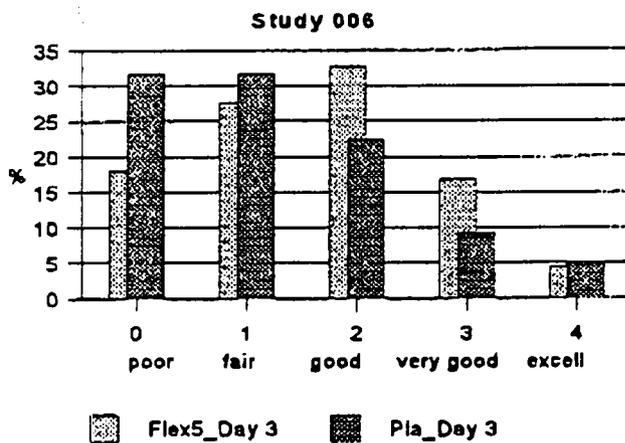
Patient Global Change - Day 3



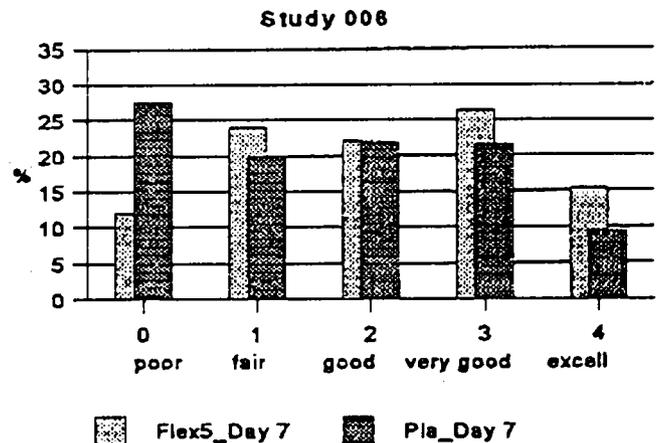
Patient Global Change - Day 7



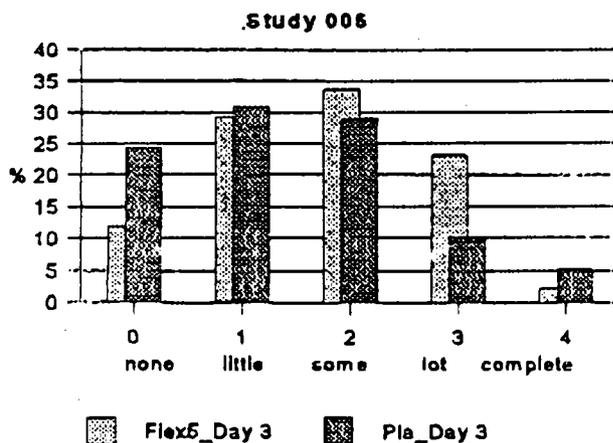
Patient Rating of Medication - Day 3



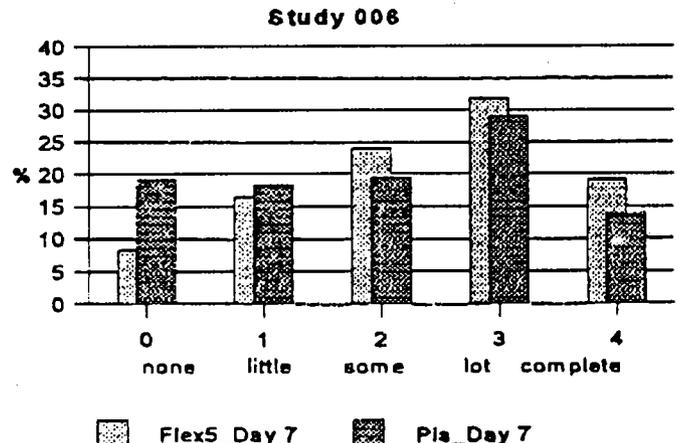
Patient Rating of Medication - Day 7



Patient Diary on Relief - Day 3



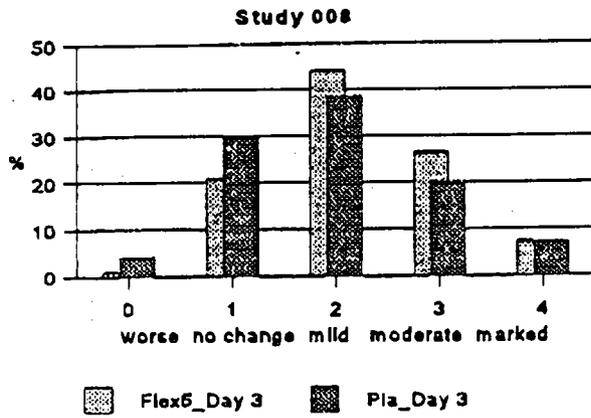
Patient Diary on Relief - Day 7



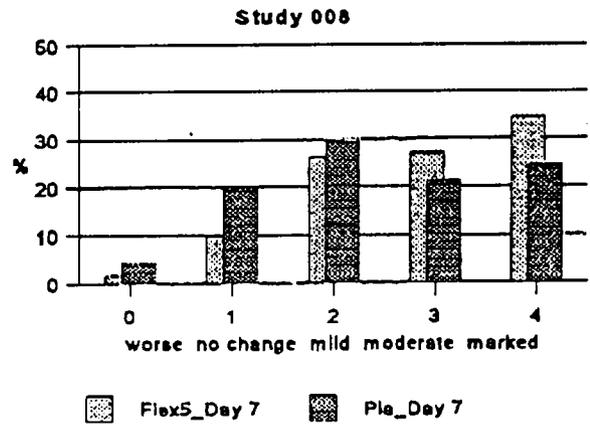
NDA 21-070 Flexeril 5 mg  
Efficacy Study 008 Distribution of Categorical Responses

Chart # 2

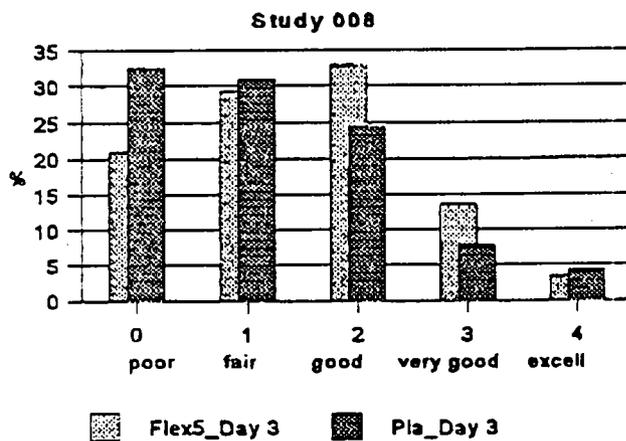
Patient Global Change - Day 3



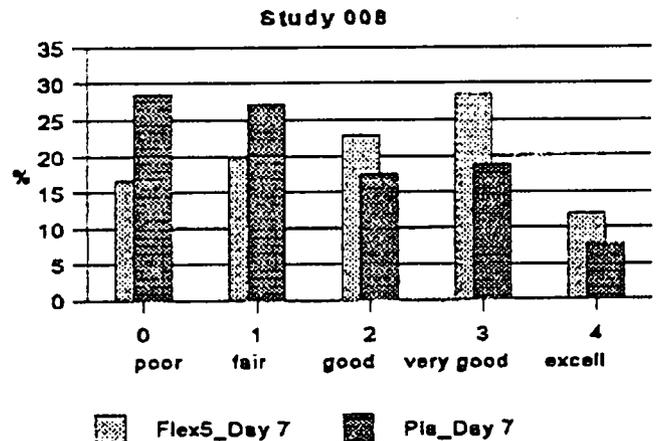
Patient Global Change - Day 7



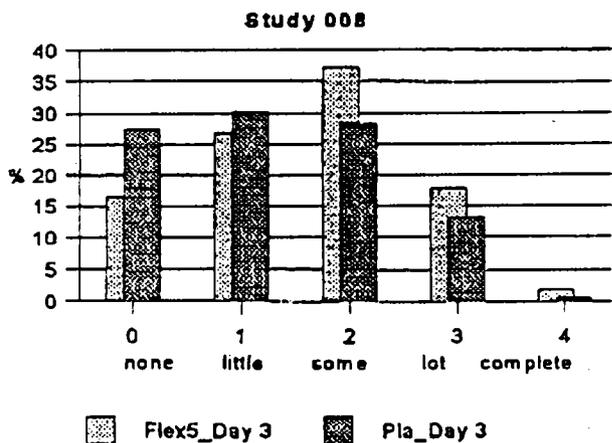
Patient Rating of Medication - Day 3



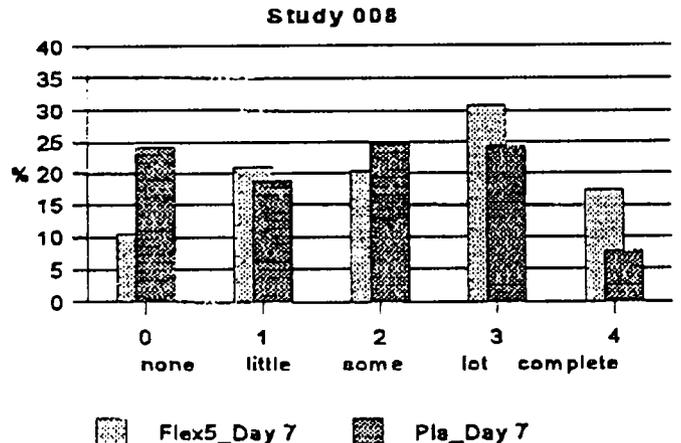
Patient Rating of Medication - Day 7



Patient Diary on Relief - Day 3



Patient Diary on Relief - Day 7



*Lillian Patrician* 6/18/99  
Lillian Patrician, MS, MBA  
Mathematical Statistician

Concur: *M. J. Huque* 6/18/99 Dr. Mohammad Huque Dr. Stan Lin

*M. J. Huque* 6/18/99  
*Stan Lin*

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HFD-725/File  
HFD-725/Huque/Lir./Patrician  
Chron.

*This summary has five [ 5 ] pages including two [ 2 ] charts.*