Minutes: July 20, 1999
Nonprescription Drugs and Arthritis Advisory Committees

Issue: Consideration of NDA 21-070, Flexeril 5mg (cyclobenzaprine HCL) Merck

Attendance:
NDAC Members Present: Eric Brass, M.D., Ph.D., Chair; Mary Anne Koda-Kimble, Pharm.D., Kathleen Hamilton, George Blewitt, M.D. (non voting), Richard Neill, M.D., Hari Sachs, M.D, Edward Krenzelok, Pharm. D., Edwin Gilliam, Ph.D.

NDAC Consultants: Carol McNeely, M.D., Ph.D., Jennifer Anderson, Ph.D., Rebat Halder, M.D.

Arthritis Members Present: Steven Abramson, M.D., Daniel Lovell, M.D., MPH, Janet Elashoff, Ph.D., Leona Malone, Frank Pucino, Pharm.D., Nigel Harris, M.D. David Yocum, M.D., Yvonne Sherrer, M.D.

Arthritis Members Absent: Kenneth Brandt, M.D., Larry Moreland, M.D., Ildy Katona, M.D.,

Guest: Lynn Gerber, M.D.

FDA Participants:
Robert DeLap, M.D., Ph.D. Charles Ganley, M.D., Karen Midthun, M.D., Linda Katz, M.D., MPH, John Hyde, M.D., Ph.D., and the reviewers listed below.

The meeting was held at the Holiday Inn in Gaithersburg, Maryland. Prior to the meeting, the members and consultants had reviewed background material from the FDA and from Merck. There were approximately 150 persons in attendance. Dr. Brass opened the meeting and Dr. Titus read the conflict of interest statement into the record.

Overview of FDA's Presentation:
James Witter, M.D., Ph.D. discussed the Background and Efficacy of the NDA. Sue-Chih Lee, Ph.D., presented a Pharmacokinetic Update. Michael Klein, Ph.D., presented an overview on abuse potential and Rosemarie Neuner, M.D., MPH, presented the evaluation of Safety. Kathryn Aikin, Ph.D reviewed Label Comprehension data and issues. Linda Katz, M.D., MPH, presented Paul Andreason's, M.D review assessing the Neurological studies in the NDA.

Overview of Merck's Presentation:
Edwin Hemwall, Ph.D., presented the introduction and concluding comments on their research. Scott Korn, M.D. reviewed the Flexeril OTC Development Program.

Open Public Hearing:
Larry Sasich from Public Citizen made a statement.

Charge to the Committee:
Linda Katz, M.D., MPH, asked the committee the following questions:

1. The data in the original NDA support the use of a Flexeril dose of 10 mg T.I.D. (in the range of 20-40 mg total daily dose) as a prescription product. In the current submission for OTC use, do both Study 006 and Study 008 demonstrate a clinically significant effect of Flexeril 5 mg T.I.D. for relief of painful muscle tightness and spasm of the back or neck due to recent strain, overuse, or minor injury? In answering this question please describe the end-points and analyses that caused you come to your conclusion.

The general agreement of the committee was that the efficacy of 5 mg of Flexeril® had not been established. Some of the concerns expressed included: (1) The efficacy measures were not robust. Pain reduction as a surrogate may not be a measure of efficacy. Sleepiness confounds the use of relying on pain reduction as a measure of efficacy. (2) The studies lacked any measures that would demonstrate that people could functionally do more because their back spasm was diminished. (3) The magnitude of the responses measured while statistically significant may have little clinical relevance. The analysis treated the pain reduction as a continuous variable where a categorical analysis might be more relevant. For instance what does a .2 difference mean? (4) By day 7 about 70% of back spasm was resolved – including those on placebo.

A view was expressed that the studies did demonstrate efficacy and that the sponsor should not be held to performance criteria.

2. Is muscle spasm of the back or neck a consumer self-diagnosable condition? In answering this question please describe the data relied upon from the application.

The prevailing opinion of the committee was that self-diagnosis was a difficult thing to assess based on the available data. Issues that were raised included: (1) Is the physician the gold standard for judging if a spasm is present? (2) Would there even be reliability among physicians? (3) In trials, physicians may be biased and concur with a person's perception in order to enroll them. (4) It is very hard for a consumer to accurately identify a back spasm by palpating in a hard to reach place. (5) It is hard to separate back pain from back spasm. (6) There are individual differences in firmness of muscles and hence it is hard to assess. (7) If we had data that said 95% with back pain had spasm, then it would be easier to believe that people could self diagnose. (8) If categorical data such as neck versus back or aged versus young were used we would know more.

The second way this question was addressed was the fact that a placebo controlled trial (like 009 with a placebo) might help to determine the efficacy in a self-diagnosed setting.

3. Can consumers identify when Flexeril should be used, as opposed to other products such as an OTC analgesics?
(a) Can they adequately assess whether their condition is responding to treatment?
(b) Were there conditions identified by a significant number of subjects where Flexeril use was considered when it should not have been?

The committee raised the issue that the studies did not assess if consumers can adequately identify when to use Flexeril® as opposed to other products such as OTC analgesics. Some of the elaboration on this theme: Since OTC products will be used in conjunction with other products committee members raised the question as to whether an incremental benefit can be demonstrated on top of the use of other products. There is a dilemma when a product goes to OTC use because people will tend to use it beyond what is written on the label.

A discussant noted that a company should not be required to do more than other companies, and that the expectation expressed on the use of other products and comparative efficacy were more than a company should be expected to do.

4. Has the metabolism and excretion of Flexeril been adequately characterized?
(a) If no, what additional information should be obtained (e.g. better characterization of the metabolic pathway, drug-drug interactions)?
(b) Are there any potential or known drug-drug or drug-food interactions that may impact on the safe use of this drug in the OTC setting?

The committee noted the lack of studies on (1) metabolic profile and enzymes responsible for this metabolism (2) screening of candidate drug interactions (pharmacokinetic and pharmacodynamic), (3) pharmacodynamic modeling, (4) use of ethnically diverse populations, and (5) limited studies on the elderly.

5. Safety concerns include the adverse reactions associated with Flexeril use (especially adverse reactions similar to those seen with closely-related tricyclic antidepressants); the possibility of misuse or overdose; and any possible drug interactions.

(a) Can consumers, including elderly individuals, safely use Flexeril in an OTC setting, taking into account the available data on adverse effects, sedation, overdose and misuse, and concomitant medications?
(b) If not, why not? If yes, is any additional information needed on the labeling?

The types of problems that consumers were likely to have: (1) May confuse tension to mean a headache and use for the wrong indication, (2) There was likely to be confusion over concomitant use of other medications that were commonly used OTC. (3) We need a better understanding of the psychomotor impairments when there is concomitant use (4) There is no psychomotor data - particularly driving assessment in days 7-10. (5) Since the sample size was so low it is hard to separate what is sedation from what is impairment. (6) Maybe the elderly should not use Flexeril® at all because of the psychomotor risks. (7) Sensitivity of studies to detect outliers demonstrating extreme impairment in response.

The committee expressed less concern about arrhythmia hallucinations in response to Flexeril®.

6. Does the Committee have any additional concerns/issues?

The committee suggested that the FDA needed to do some studies itself on the impact of labeling and whether consumers follow the advice. Committee members felt that worrying about specific language in the absence of a real study of consumer behavior was not particularly helpful.

A verbatim transcript of this meeting will be available on the FDA's Dockets Management Branch Website approximately 30 days after the meeting. The address is HTTP://www.fda.gov/ohrms/dockets/ac/acmenu.htm.

I certify that I attended the July 20, 1999 joint advisory committee meeting and that these minutes accurately reflect what transpired.

Sandra Titus 7/30/99

Sandra Titus, Ph. D
Executive Secretary, NDAC

Eric Brass, M.D., Ph.D.
Chair NDAC