Meeting of the Urology Subcommittee to the Advisory Committee of Reproductive Health Drugs Advisory Committee

Meeting Date: April 10, 2000

New Drug Application NDA 21-118, Uprima (apomorphine HCl tablets, sublingual) Tap Holdings, Inc.

Proposed Indication: For use in the treatment of erectile dysfunction.

Meeting location: Holiday Inn, Bethesda, Maryland.

Meeting time: The subcommittee was called to order by the chairman, Dr. Ricardo Azziz at approximately 9:00 a.m. The meeting was adjourned at approximately 4:00 p.m.

Attendance: A total of approximately 250 persons were in attendance.
Urology Advisory Subcommittee members present: 13 subcommittee members were in attendance. Of these, three members of the Advisory Committee for Reproductive Health Drugs were present: Ricardo Azziz, M.D., M.P.H., Michael Greene, M.D. and Julia Scott, R.N. (consumer representative). The following non-committee, subcommittee member were present: one statistician: Ralph D'Agostino, Ph.D. ; three cardiologists:Robert Califf, M.D., Peter Kowey, M.D. and Thomas Graboys, M.D.; five urologists: Phillip Hanno, M.D., Marguerite Lippert, M.D., Craig Donatucci, M.D., Stephen Jacobs, M.D. and Michael O'Leary, M.D.; one sex researcher/therapist: Leonore Tiefer, Ph.D.

Subcommittee Voting privileges: All subcommittee members were Special Government Employees (SGEs) and were approved to vote on the three questions posed to the subcommittee.

FDA Speakers/Participants: Victor Raczkowski, M.D., Marianne Mann, M.D, Daniel Shames, M.D., Mark Hirsch, M.D., Venkateswar Jarugula, Ph.D.

Background Packages: Both sponsor and FDA background packages were forwarded to the subcommittee members for review prior to the meeting. The

sponsor package and a redacted version of the FDA package were placed on the FDA dockets web-site one business day prior to the meeting.

Summary of Tap Pharmaceuticals Presentation:
James Freston, M.D., Ph.D. of the University of Connecticut Health Center (Tap consultant) provided an introduction to the Tap presentation. Barbara Bopp, Ph.D., Manager, Drug Metabolism and Pharmacology, described the drug pharmacokinetics and metabolism. Jeremy Heaton, M.D., Professor, Queens University, Ontario, Canada (Tap consultant) presented an overview of erectile dysfunction treatments and provided a summary of the Uprima efficacy studies. Dr. Freston provided a summary of Uprima safety and an assesment and summary of benefit-risk for Uprima.

Summary of FDA Presentation: Daniel Shames,M.D., Urology Team Leader (DRUDP), provided an introductory overview to the FDA presentation. Venkasteswar Jarugula, Ph.D., Clinical Pharmacology and Biopharmaceutics Reviewer (DRUDP), described the drug pharmacokinetics and drug-alcohol interaction studies. Mark Hirsch, M.D., Medical Officer (DRUDP), presented the clinical safety and efficacy and Marianne Mann, M.D., Deputy Director (DRUDP), described the drug-antihypertensive interactions along with a summary of the agency presentation, the points to consider and questions presented to the subcommittee by the agency.

Open Public Hearing:
One patient who participated in the Phase III clinical trials with Uprima™ spoke regarding his experience using Uprima™. The speaker disclosed to the sub-committee that Tap Pharmaceuticals invited him to testify and that Tap is re-imbursing him for his travel expenses.

The subcommittee discussed the following "Points to Consider" and voted on the following questions:

Points to Consider:

A. Selective population studied
B. Clinical relevance of efficacy results
C. Safety concerns
   Adverse events (hypotenson and syncope)
   Alcohol interaction
   PK variability
   Antihypertensive interaction
D. Use in real life

Questions:

1. Does the patient population studied support the proposed indication "for the treatment of erectile dysfunction"?

   If yes, please elaborate.

   If no, please describe your concerns.

   Vote: Yes: 13 No: 0

   Subcommittee Discussion: Several of the subcommittee members qualified their "yes" vote. They stated that the labeling of the product should succinctly and completely describe the patient populations excluded from the clinical studies.

2. Do the date presented support an acceptable risk:benefit profile for the 2 mg dose of Uprima™?

   If yes, please elaborate.

   If no, please describe your concerns, including additional studies that might address these concerns.

   Vote: Yes: 10 No: 2

   (*Note, prior to the subcommittee votes on questions no. 2 and 3, Dr. Thomas Graboys exited the subcommittee meeting).

   Subcommittee Discussion: The subcommittee strongly urged the Agency to include cautionary text in the professional label regarding the use of the product with alcohol, food, nitrate containing or other cardiovascular products and the resultant adverse events seen following their concomitant use with the product. The committee referred specifically to the development of hypotension, syncopy, nausea and vomiting. The concensus of the subcommittee was that this text preferably take form of a contraindication or black boxed warning. The subcommittee also strongly urged the Agency to require that dispensation of the product be accompanied by patient labeling. The patient labeling should include detailed instructions for safe use of the product and cautionary information regarding the potential for development of adverse effects.

3. Do the data presented support an acceptable risk:benefit profile for the 4 mg dose of Uprima™?

   If yes, please elaborate.

   If no, please describe your concerns, including additional studies that might address these concerns.

   Vote: Yes: 9 No: 3

   Subcommittee discussion: The subcommittee concerns with the risk:benefit ratio of the 4 mg dose mirrored those expressed during the discussion of the 2 mg dose. As with the 2 mg dose, the subcommittee expressed their opinion that the risk concerns could be addressed adequately in the professional and patient labeling for the product. Members of the subcommittee specifically recommended that text regarding use of the product with alcohol, food, nitrates and other cardiovascular medications be included. In addition, the subcommittee discussed the issue of whether the first dose of the drug should be limited to use in the physician's office. The concensus of the subcommittee was that limiting its first use to the physician's office was not necessary.

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.

Created on: April 11, 2000
Created by: Jayne E. Peterson, R.Ph., J.D.
Executive Secretary, Urology Advisory Subcommittee to the Advisory Committee for Reproductive Health Drugs

I certify that I attended the April 10, 2000 meeting of the Urology Subcommittee to the Advisory Committee for Reproductive Health Drugs and that these minutes accurately reflect what transpired.

Jayne E. Peterson, R.Ph.,J.D.
Executive Secretary, ACRHD

Ricardo Azziz, M.D.
Chair, ADRHD