CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: ANESTHETIC AND LIFE SUPPORT DRUGS ADVISORY COMMITTEE

DATE OF MEETING: 09/17/97

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SUMMARY MINUTES

Food and Drug Administration
Center for Drug Evaluation and Research

SUMMARY MINUTES OF THE ANESTHETIC AND LIFE SUPPORT DRUGS ADVISORY COMMITTEE

September 17, 1997
Gaithersburg Hilton - Gaithersburg, MD

Members Present
John B. Downs, M.D., Chair
Amanda S. Carlisle, Ph.D., M.D.
John E. Ellis, M.D.
Terese T. Horlocker, M.D.
Edward Lowenstein, M.D.
Susan K. Palmer, M.D.
Charles A. Rohde, Ph.D.
John J. Savarese, M.D.
Mehenoor Watcha, M.D.
Paul F. White, Ph.D., M.D.
Margaret Wood, M.D.
Marie L. Young, M.D.

Consumer Representative
Mary G. Curll, R.N., M.S.N., CNOR

Consultants to the FDA
Suzanne T. Brown, CRNA
Harriet DeWit, Ph.D. (DAAC)
Ronny Hertz, M.D.
Laura McNicholas
Mitchell Max, M.D.
Derek Raghavan, M.D. (ODAC)
Peter Rothstein, M.D.
Eric C. Strain, M.D. (DAAC)

FDA Participants
Cynthia G. McCormick, M.D.
Curtis Wright, M.D.
Roberta C. Kahn, M.D.
Suresh Doddapaneni, Ph.D.
Michael Klein, Ph.D.
Promoda Mataru, Ph.D., M.B.A.

Executive Secretary
Karen M. Templeton-Somers, Ph.D.

Member Not Present
Joseph Reves, M.D.

Sponsor Participants
Steven A. Shoemaker, M.D.
Russell K. Portenoy, M.D.
Clair Callan, M.D., M.B.A.

These summary minutes for the September 17, 1997 meeting of the Anesthetic and Life Support Drugs Advisory Committee were approved on January 22, 1998.

I certify that I attended the September 17, 1997 Committee meeting and that these minutes accurately reflect what transpired.

Karen M. Templeton-Somers
Karen M. Templeton-Somers, Ph.D.
Executive Secretary

John B. Downs
John B. Downs, M.D.
Chairman

On September 17, 1997, the Anesthetic and Life Support Drugs Advisory Committee met at The Hilton, 620 Perry Parkway, Gaithersburg, MD to discuss NDA 20-747 Actiq™ (oral transmucosal fentanyl citrate drug matrix on a handle), from Anesta Corp., for the management of chronic pain, particularly breakthrough pain, in patients who are already receiving and are tolerant to opioid therapy. The meeting commenced at 8:37 a.m. with the Call to Order by Committee Chair John B. Downs, M.D., and the introduction of meeting participants. The conflict of interest statement was read by Karen M. Templeton-Somers, Ph.D., Executive Secretary. The meeting was attended by approximately 120 persons.

The following people made presentations at the Open Public Hearing:

Carol Curtiss, RN,MSN, OCN, Clinical Nurse Specialist Consultant
Sharon Weinstein, M.D., for the American Alliance of Cancer Pain Initiatives
Mary A. Simmonds, M.D., for the American Cancer Society
Jacob Sitlinger, cancer patient
Anthony Mercantino, cancer patient

All presentations at the Open Public Hearing emphasized the need for products to help in the management of cancer pain and were in support of NDA 20-747, Actiq™, from Anesta Corp.

Dr. Cynthia McCormick, M.D., Director of the Division of Anesthetic, Critical Care and Addiction Drugs Products presented the Opening Remarks and Introduction for the FDA. The Committee was asked to consider the magnitude of the clinical effect demonstrated in the sponsor's studies and the safety profile of the drug in both cancer pain trials and in the opiate-naive population. The management of potential public risk of this product is a major concern, as the population at greatest risk of adverse effects is dissociated from the population that would benefit from its approval.

Sponsor's Presentations:

Background of OFTC and Actiq™ Indication	Steven Shoemaker, M.D. Vice President, Medical Communications Anesta Corp.
Actiq™ Clinical Program	Russell Portenoy, M.D. Chairman, Dept. of Pain Medicine and Palliative Care Beth Israel Medical Center, NY
Safety Review	Steven Shoemaker, M.D.
Risk Management Program	Clair Callan, M.D., MBA VP, HPD, Medical, Regulatory Affairs and Advanced Research Abbott Laboratories

Actiq™ is a product designed for the management of breakthrough pain, and consists of a solid drug matrix, containing the opioid fentanyl, and attached to a handle marked with the dose strength. Fentanyl is absorbed quickly across the oral mucosa. Meaningful pain relief is obtained quickly and is of relatively short duration. The most common treatment-related adverse events among chronic pain patients were nausea, somnolence and dizziness. Dose-dependent respiratory depression was seen in the opioid non-tolerant population.

The risk management program centers on child safety, the safety of the non-tolerant population and the diversion and abuse potential of Actiq. Planned procedures for preventing child access risk include the use of individually sealed, child-resistant pouches, multiple dose strengths for total unit consumption and specific disposal instructions. Programs proposed to prevent misuse and abuse include educational materials at the doctor, pharmacist and patient level, post-market surveillance and an audit and response plan.

FDA Presentations:

Pharmacokinetics	Suresh Doddapeneni, Ph.D. Pharmacokineticist
Clinical Review - Efficacy	Curtis Wright, M.D. Deputy Director, DACCADP
Clinical Review - Safety	Roberta Kahn, M.D. Medical Officer
Abuse Liability	Michael Klein, Ph.D. Team Leader, Abuse Liability
Risk Management Plan	Curtis Wright, M.D.

The risk of respiratory depression in the chronic pain population cannot be ruled out with the data from the sponsor's current studies. Other adverse effects that are characteristic of fentanyl include somnolence, dizziness and confusion. When used in an at-home, unmonitored environment, patient safety and medication disposal become important concerns. The risk management plan includes five elements: control of promotion, prescription and distribution; warnings to all parties; specific instructions; surveillance and intervention. The total plan must reduce the risk of accidental or iatrogenic toxicity to a level where the benefits to the intended users outweigh the risk to the rest of the patients and the public.

The meeting proceeded with Committee discussion and questions about the FDA and Sponsor presentations, before breaking for lunch.

After lunch, there was an interactive discussion of the balancing of the issues of safety and risk management with the intense need for improved, rapid onset and non-invasive medications for severe pain. The second Open Public Hearing took place, with Carl F. Dixon presenting on behalf of the National Kidney Cancer Association, and in support of the product. The Committee

discussion resumed and concluded with a vote on the question., "Does the expected benefit to the intended clinical population outweigh the risk of accidental injury inherent in this product?"

VOTE: Yes - 19 No - 0

During the vote, the Committee made a number of recommendations designed to reduce the risk of the product, including:

- extensive education programs regarding the safe use of this product.

- improvements to the product labeling. Recommendations include a graphic to indicate the toxicity to children, better definition of the label term "opioid-tolerant", more legible and informative marking on the handle, and larger type in the package insert.

- close surveillance of the product post-marketing, with plans in place for rapid action in case of reports of accidental poisoning or suspected abuse. Plans should be in place for immediate investigation and extensive data collection upon the occurrence of poisonings. More data is also necessary on the associated adverse events, including possible hypoventilation.

- development of a plan for retrieving unused medication and an incentive program for proper disposal.

- improvements to the risk management plan. Quantitative and timely post-market information is necessary to measure the risk of this product. A toll-free phone number could be used for questions and the report of problems. The sponsor could consider making an opioid agonist available to the families of patients, for use in case of accidental poisoning.

The Committee was thanked for their thoughtful consideration and the meeting was adjourned at 4:12 p.m.

Karen M. Templeton-Somers, Ph.D.
Executive Secretary
Anesthetic and Life Support Advisory Committee

APPEARS THIS WAY
ON ORIGINAL