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Summary Minutes of the
the Joint Meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee
August 20, 2010

Location: Bethesda Marriott, The Ballrooms, 5151 Pooks Hill Road, Bethesda, Maryland.

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information office.

A verbatim transcript will be available in approximately two-four weeks, sent to the Division and posted on the FDA website at:
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisDrugsAdvisoryCommittee/ucm203434.htm

These summary minutes for August 20, 2010 Joint Meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee were approved on September 13, 2010

I certify that I attended the August 20, 2010, joint meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee and that these minutes accurately reflect what transpired.

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Anuja Patel, M.P.H.
Designated Federal Official, AAC

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Kathleen O’Neil, M.D.
Committee Chair
The Arthritis Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee met on August 20, 2010 at the Bethesda Marriott, The Ballrooms, 5151 Pooks Hill Road, Bethesda, Maryland. Prior to the meeting, members and invited consultants were provided copies of the background material from the FDA. The meeting was called to order by Kathleen O’Neil, M.D. (Committee Chair); the conflict of interest statement was read into the record by Anuja Patel, M.P.H. (Designated Federal Official). There were approximately 250 persons in attendance. There were sixteen (16) speakers for the Open Public Hearing session.

**Issue:** On August 20, 2010, the committees discussed new drug application (NDA) 22-531, sodium oxybate, 375 milligrams per milliliter (mg/ml) oral solution, sponsored by Jazz Pharmaceuticals, with a proposed indication for the treatment of fibromyalgia for patients 18 years of age and older. The safety and efficacy findings for sodium oxybate in the fibromyalgia population and the proposed Risk Evaluation and Mitigation Strategy (REMS) for this product was discussed.

**Attendance:**
**Arthritis Advisory Committee Members Present (Voting):**
Diane Aronson *(Consumer Representative)*, Lenore Buckley, M.D., M.P.H., Robert Kerns, Ph.D., Ted Mikuls, M.D., M.S.P.H., Nancy Olsen, M.D., Kathleen O’Neil, M.D. *(Chair)*

**Drug Safety and Risk Management Advisory Committee Members Present (Voting):**
Lewis Nelson, M.D., Allen Vaida, Pharm. D., FASHP, Sidney Wolfe, M.D. *(Consumer Representative)*

**Non-voting Participants:**
Mark Fletcher, M.D. *(Arthritis Advisory Committee Industry Representative)*
William Z. Potter, M.D., Ph.D. *(Psychopharmacologic Drugs Advisory Committee Industry Representative)*

**Temporary Voting Members:**
Barbara Berney *(Patient Representative)*, William Cooper, M.D., M.P.H., Ruth S. Day, Ph.D., Richard Denisco, M.D., M.P.H., Dennis Dixon, Ph.D., Sheldon Kapen, M.D., Jeffrey E. Kirsch, M.D., Thomas Kosten, M.D., John Markman, M.D., Richard Meisch, M.D., Ph.D., Cynthia Morris-Kukowski, Mary Ellen Olbrisch, Ph.D., ABPP, Charles Rohde, Ph.D.

**Arthritis Advisory Committee Members Not Present:**
David E. Blumenthal, M.D., Christy Sandborg, M.D., Robert Stine, Ph.D.

**Drug Safety and Risk Management Advisory Committee Members Not Present:**
Elaine Morrato, Dr. P.H.

**FDA Participants (Non-Voting):**
Bob Rappaport, M.D., Sharon Hertz, M.D., Ellen Fields, M.D., M.P.H., Henry Francis, M.D., Mary Willy, Ph.D.

**Open Public Hearing Speakers:**
1. Lynn Matallana *(National Fibromyalgia Association)*
2. Rita Ann Campbell
3. Jan Mathies
4. Jennie Blauvelt
5. Victor Rosenfeld, M.D. *(South Coast Medical Group)*
6. Trinka Porrata *(Project GHB)*
7. Deanna Power *(Sansum Clinic)*
8. Linda Zeman
10. Muhammed B. Yunus, M.D.
11. Susan Christ
12. Gregory Backes
13. Barbara Gehr
14. Alex Stalcup, M.D. *(New Leaf Treatment Center)*
15. Jennifer E. Wilson
16. Evan F. Ekman, M.D.
The agenda was as follows:

Call to Order
Kathleen O’Neil, MD
Chair, AAC

Conflict of Interest Statement
Anuja Patel, MPH
Designated Federal Officer

Opening Remarks
Ellen Fields, M.D., M.P.H.
Clinical Team Leader
Division of Anesthesia and Analgesia Products (DAAP)
Office of Drug Evaluation (ODE) II, CDER, FDA

Sponsor Presentations:

Introduction
Janne Wissel
Chief Regulatory and Compliance Officer
Jazz Pharmaceuticals, Inc.

Unmet Medical Need
Jon Russell, Ph.D., M.D., ACR Master
Associate Professor of Medicine
Director, University Clinical Research Center
The University of Texas Health Science Center at San Antonio

Efficacy Overview
Diane Guinta, Ph.D.
Vice President, Clinical Development and Scientific Affairs
Jazz Pharmaceuticals, Inc.

Safety Overview
Annette Madrid, M.D.
Chief Medical Officer
Jazz Pharmaceutical, Inc.

REMS
Janne Wissel
Chief Regulatory and Compliance Officer
Jazz Pharmaceutical, Inc.

Clinicians’ Perspectives
Michael Spaeth, M.D.
Specialist, Center for Clinical Rheumatology
Practice for Internal Medicine and Rheumatology
Munich-Graefelfing, Germany

FDA Presentations:

Safety and Efficacy,
Post-marketing Data,and
Currently Approved
Fibromyalgia Products
Elizabeth Kilgore, M.D.
Medical Officer
DAAP, ODE II, CDER, FDA

David Petullo, M.S.
Statistical Reviewer
Division of Biometrics II
Office of Biostatistics, CDER, FDA
Committee voting, discussion, and recommendations:

Questions to the Committee:

1. Discuss whether the data that have been submitted are adequate to demonstrate that sodium oxybate is effective in the treatment of fibromyalgia. Are additional data needed? If so, of what type?

   Overall the committee agreed that data demonstrated efficacy in the fibromyalgia population; however, the committee was concerned that the effect was modest in many patients and the effect may only reach a subset of patients. There was also concern on whether an adequate control was used by the sponsor’s study in order for it to be a true blinded study. The committee would like to see additional data including comparative data with currently approved products used to treat fibromyalgia, data on vulnerable populations including individuals on poly-pharmacy and patients with a number of common co-morbidities in the fibromyalgia population, long term safety and efficacy data beyond 52 weeks, pre and post drug treatment outcomes data on cognitive functioning, and data on adjunctive pain medications.

   Please see transcript for additional details.

2. Discuss whether the data that have been submitted are adequate to demonstrate that sodium oxybate improves sleep in fibromyalgia patients. Are additional data needed? If so, of what type?

   Overall, the committee felt that the data submitted for the sleep claim were convincing but there were strong methodological weaknesses in the definitions of sleep improvement and the self reported study. A suggestion was made to include daily diaries instead of monthly reporting by patients. Hence, the panel felt that the data provided were not strong enough to support the sleep claim.

   Please see transcript for additional details.

3. Is the Sponsor’s proposed REMS sufficient to address the potential for medication errors, misuse, and abuse of the product considering the widely expanded use of sodium oxybate that is expected once the product has been approved for the treatment of fibromyalgia? Consider the following when discussing this question:
Question 3 Continued-

a. The Sponsor has proposed a different brand name and a different concentration for this product from that of their currently marketed product Xyrem.

b. The Sponsor has not included the collection and evaluation of safety-related data as part of the REMS. Please consider whether this should be required as part of a post-marketing evaluation program.

The committee strongly advised the Agency and Sponsor to use a single brand name, single concentration, and single REMS for the two indications. The committee expressed concern with the dispensing tool and the potential for misuse (under-dosing and over-dosing) by patients and the potential risk of harm for households with children. The committee expressed a major concern with the use sodium oxybate and its effect in patients taking CNS medications and/or with alcohol intake. In addition, the committee was concerned with the misuse and abuse potential for this drug and the lack of diagnostic tools for emergency health professionals. The committee was concerned with the wide availability of sodium oxybate on the street once fibromyalgia patients start receiving the drug through their physician.

Please see transcript for additional details.

c. Is the Sponsor’s proposal for two similar but separate risk management programs (e.g., separate prescriber and patient enrollment, specialty pharmacies, and educational materials) for each indication sufficient to address the potential for medication errors? Will these two programs increase the burden on the healthcare system?

The committee overwhelmingly expressed concern that the Sponsor should have a single risk management program and an adequate patient education program in place. Having two risk management programs will produce a burden on the healthcare system and the responsibility of dispensing pharmacist will increase.

Please see transcript for additional details.

d. Should the REMS address the potential of concomitant use of CNS depressants and/or alcohol?

The committee strongly agreed with the Agency and would like to have REMS address the potential of concomitant use of CNS depressants and/or alcohol.

Please see transcript for additional details.

4. Should the Agency issue a post marketing requirement (PMR) for safety assessment?

a. Should the Agency require the collection and evaluation of safety-related data as a post marketing requirement, similar to the “post marketing evaluation program” that was required when sodium oxybate was initially approved? If so, what data should be collected?

Committee members felt strongly that the drug, if approved, will affect a much larger treatment population that includes adolescents. The committee cautioned the Agency that monitoring will be challenging as there is no diagnostic tool available to identify sodium oxybate/GHB abuse, etc. The PMR for safety assessment will have to be stricter than when sodium oxybate was initially approved. The abuse and over use of drug will need to be monitored. In addition, the committee felt that there was a lack of adequacy of education to the patient population.

Please see transcript for additional details.
5. **VOTING QUESTION:** Does the risk/benefit balance favor approval of sodium oxybate for the treatment of fibromyalgia? *(YES/NO/ABSTAIN)*

   YES= 2    NO= 20    ABSTAIN= 0

If not, what additional efficacy or safety data, or changes or additions to the proposed risk mitigation strategy should be required?

*The committee requested additional information on efficacy and cognitive functioning. In addition, the committee requested comparative studies and studies with patients on other pain medications and comorbidities. Some members were concerned with the integrity of the efficacy studies presented and the generalizability of the data presented by the Sponsor. The committee unanimously agreed that the proposed risk mitigation strategy was inadequate and needed to be improved as a larger population may have access to the drug.*

*The meeting adjourned at 4:30 p.m.*