

**Food and Drug Administration
Center for Drug Evaluation and Research**

**Summary Minutes of the Joint Meeting of the Anesthetic and Analgesic Drug Products
Advisory Committee and the Drug Safety and Risk Management Advisory Committee
February 14, 2018**

Location: FDA White Oak Campus, Building 31 Conference Center, The Great Room (Rm. 1503), 10903 New Hampshire Ave, Silver Spring, Maryland.

Topic: The committees were asked to discuss new drug application (NDA) 209257, proposed tradename, HYDEXOR, a fixed-dose combination oral tablet, submitted by Charleston Laboratories, Inc., that contains hydrocodone, acetaminophen, and promethazine, for the short-term management of acute pain severe enough to require an opioid analgesic while preventing and reducing opioid-induced nausea and vomiting. The committees were also asked to discuss the abuse potential of this non-abuse-deterrent product and whether it should be approved.

These summary minutes for the February 14, 2018, joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration were approved on April 4, 2018.

I certify that I attended the February 14, 2018, joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

_____/s/_____
Moon Hee V. Choi, PharmD
Designated Federal Officer, AADPAC

_____/s/_____
Mary Ellen McCann, MD, MPH
Acting Chairperson, AADPAC

**Summary Minutes of the Joint Meeting of the Anesthetic and Analgesic Drug Products
Advisory Committee and the Drug Safety and Risk Management Advisory Committee
February 14, 2018**

The following is the final report of the joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee, held on February 14, 2018. A verbatim transcript will be available in approximately six weeks, sent to the Division of Anesthesia, Analgesia, and Addiction Products, the Office of Surveillance and Epidemiology, and posted on the FDA website at:

<https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/ucm591101.htm> and
<https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/ucm591104.htm>.

All external requests for the meeting transcript should be submitted to the CDER Freedom of Information Office.

The Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on February 14, 2018, at the FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Charleston Laboratories, Inc. The meeting was called to order by Mary Ellen McCann, MD, MPH, (Acting Chairperson). The conflict of interest statement was read into the record by Moon Hee Choi, PharmD (Designated Federal Officer). There were approximately 135 people in attendance. There were three Open Public Hearing (OPH) speaker presentations.

Issue: The committees were asked to discuss new drug application (NDA) 209257, proposed tradename, HYDEXOR, a fixed-dose combination oral tablet, submitted by Charleston Laboratories, Inc., that contains hydrocodone, acetaminophen, and promethazine, for the short-term management of acute pain severe enough to require an opioid analgesic while preventing and reducing opioid-induced nausea and vomiting. The committees were also asked to discuss the abuse potential of this non-abuse-deterrent product and whether it should be approved.

Attendance:

Anesthetic and Analgesic Drug Products Advisory Committee Members Present (Voting):

Brian T. Bateman, MD, MSc; David S. Craig, PharmD; Jeffrey L. Galinkin, MD, FAAP; Jennifer G. Higgins, PhD (Consumer Representative); Ronald S. Litman, DO; Mary Ellen McCann, MD, MPH (Acting Chairperson); Abigail B. Shoben, PhD; Kevin L. Zacharoff, MD, FACIP, FACPE, FAAP

Anesthetic and Analgesic Drug Products Advisory Committee Members Not Present

(Voting): Raeford E. Brown, Jr., MD, FAAP, Lonnie Zeltzer, MD

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Anesthetic and Analgesic Drug Products Advisory Committee Member Not Present (Non-Voting): W. Joseph Herring, MD, PhD (Industry Representative)

Drug Safety and Risk Management Advisory Committee Members Present (Voting): Niteesh K. Choudhry, MD, PhD; Laurel A. Habel, MPH, PhD; Steven B. Meisel, PharmD; Suzanne B. Robotti (Consumer Representative); Anne-Michelle Ruha, MD, FACMT; Terri L. Warholak, PhD, RPh, CPHQ, FAPhA

Drug Safety and Risk Management Advisory Committee Members Not Present (Voting): Kelly Besco, PharmD, FISMP, CPPS; Denise M. Boudreau, PhD, RPh; Christopher H. Schmid, PhD; Soko Setoguchi, MD, DrPh; Almut Winterstein, RPh, PhD, FISPE (Chairperson)

Drug Safety and Risk Management Advisory Committee Member Not Present (Non-Voting): Linda Scarazzini, MD, RPh (Industry Representative)

Temporary Members (Voting): Cynthia L. Arfken, PhD; Daniel Ciccarone, MD, MPH; Margaret Kotz, DO; Edward Michna, MD, JD, RPh; Elaine H. Morrato, DrPH, MPH; Laura D. Porter, MD (Patient Representative); Trivellore Raghunathan, PhD

Acting Industry Representative to the Anesthetic and Analgesic Drug Products Advisory Committee (Non-Voting): Michele Hummel, PhD, RPh (Acting Industry Representative)

FDA Participants (Non-Voting): Sharon Hertz, MD; Ellen Fields, MD, MPH; Judy Staffa, PhD, RPh; Jana McAninch, MD, MPH, MS

Designated Federal Officer (Non-Voting): Moon Hee V. Choi, PharmD

Open Public Hearing Speakers: Stephanie Fox-Rawlings, PhD (National Center for Health Research); Paul Lorenc, MD, FACS; Theresa Mallick-Searle, MS, RN-BC, ANP-BC

The agenda was as follows:

Call to Order and Introduction of Committee

Mary Ellen McCann, MD, MPH
Acting Chairperson, AADPAC

Conflict of Interest Statement

Moon Hee V. Choi, PharmD
Designated Federal Officer, AADPAC

FDA Opening Remarks

Sharon Hertz, MD
Director
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP), Office of Drug Evaluation II (ODE-II)
Office of New Drugs (OND), CDER, FDA

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APPLICANT PRESENTATIONS

Charleston Laboratories, Inc.

Introduction: Today's Purpose

Thomas Smith, MD
Chief Medical Officer
Charleston Laboratories, Inc.
Jupiter, Florida

Need for New Approach to Treat Acute Pain While Preventing and Reducing OINV

Tong Joo (TJ) Gan, MD, MBA, MHS, FRCA
Professor and Chairman
Department of Anesthesiology
Stony Brook University School of Medicine
Stony Brook, New York

Abuse Potential & Human Abuse Liability

Sandra D. Comer, PhD
Professor of Neurobiology
College of Physicians and Surgeons
Columbia University
New York, New York

Clinical Development and Efficacy

Bernard P. Schachtel, MD
Chief Scientific Officer
Charleston Laboratories, Inc.
Jupiter, Florida

Clinical Safety, Responsible Use & Benefit-Risk Assessment

Thomas Smith, MD

Clarifying Questions

FDA PRESENTATIONS

Clinical Considerations in the Evaluation of the Safety and Effectiveness of Hydexor

Timothy Jiang, MD, PhD
Clinical Reviewer
DAAAP, ODE-II, OND, CDER, FDA

Utilization Patterns for Combination Hydrocodone-Acetaminophen, Selected Opioid Analgesics, and Promethazine-Containing Products

LCDR Jennie Z. Wong, PharmD
Drug Utilization Analyst
Division of Epidemiology II (DEPI-II)
Office of Pharmacovigilance and Epidemiology (OPE)
Office of Surveillance and Epidemiology (OSE)
CDER, FDA

Postmarketing Data on Misuse and Abuse of Hydrocodone and Promethazine

Jana McAninch, MD, MPH, MS
Senior Medical Epidemiologist
Prescription Drug Abuse Team
DEPI-II, OPE, OSE, CDER, FDA

Summary of FDA Findings

Ellen Fields, MD, MPH
Deputy Director
DAAAP, ODE-II, OND, CDER, FDA

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Clarifying Questions

BREAK

OPEN PUBLIC HEARING

Charge to the Committee

Sharon Hertz, MD

Questions to the Committee/
Committee Discussion

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION:** Does the Applicant's clinical program support the safe and effective use of Hydexor as an analgesic and for prevention of opioid-induced nausea and vomiting (OINV) that is limited to use in individuals likely to experience OINV?

Committee Discussion: The majority of the committee did not agree that the Applicant's clinical program support the safe and effective use of Hydexor as an analgesic and for prevention of opioid-induced nausea and vomiting (OINV) that is limited to use in individuals likely to experience OINV. Most committee members agreed that a fixed dose combination limits the ability to tailor the dose of the drug based on an individual's needs, thus reducing clinical flexibility. Some committee members noted that the risk of adverse events and unintentional overdose associated with promethazine in the combination product outweighs the little benefit shown in the data. Please see the transcript for details of the committee discussion.

2. **DISCUSSION:** There are currently no immediate-release, hydrocodone-acetaminophen combination products with abuse-deterrent properties that are approved and on the market. Do you have concerns that Hydexor does not have abuse-deterrent properties?

Committee Discussion: Some committee members stated that they did not have concerns that Hydexor does not have abuse-deterrent properties since the current abuse-deterrent formulations do not seem to be making much of an impact and that there is not much evidence of abuse of hydrocodone combination products and promethazine. One committee member noted concerns that Hydexor could be a gateway for drug abuse for those individuals that experienced OINV and questioned the applicant's commitment to risk mitigation, stating that Hydexor packaging encourages round-the-clock use and that a well-formulated risk mitigation plan need to be implemented. Please see the transcript for details of the committee discussion.

3. **DISCUSSION:** Epidemiological data suggest that misuse and abuse of promethazine, either alone or in combination with opioids or other drugs, have resulted in emergency department

visits, contact with poison control centers, and deaths. Please discuss whether you think Hydexor poses greater risks than currently-marketed hydrocodone-acetaminophen products.

Committee Discussion: *Overall, the majority of the committee agreed that Hydexor poses greater risks than currently marketed hydrocodone-acetaminophen products. Some committee members added that the proposed fixed-dose combination includes 7.5 mg of hydrocodone, which is higher than the usual starting dose of this drug. Also, the presence of promethazine could result in additional adverse events and drug-drug interactions that would not be experienced with the currently marketed hydrocodone-acetaminophen products. Some committee members noted that although there would be some misuse and abuse of Hydexor, the risk of serious promethazine toxicity, hospitalization or death with the currently suggested packaging would be low. The committee generally agreed that the benefits of Hydexor did not outweigh the risks. Please see the transcript for details of the committee discussion.*

4. **VOTE:** Should Hydexor be approved?

Vote Result: Yes: 2 No: 19 Abstain: 0

Committee Discussion: *The majority of the committee agreed that Hydexor should not be approved. Some of the committee members who voted “No” stated that their vote was based on the lack of dosing flexibility and that the ramifications of the risks associated with Hydexor did not outweigh its benefit. Some committee members added that an antiemetic may not be needed for every dose of analgesic, and that a fixed-dose combination of Hydexor would expose patients to unnecessary side effects of promethazine when it is not needed. Other committee members agreed that the applicant’s proposed risk mitigation strategies are not convincing. One committee member who voted “Yes” viewed Hydexor as another opioid option and noted that its risks are no greater than what is currently on the market. Additionally, this member noted that that the population receiving Hydexor would be those who were prone to OINV and that the medication would be taken as needed. The other committee member who voted “Yes” stated that the overall benefits outweighed the risks but also suggested that toxicity data of promethazine when patients took more than six pills a day is needed. Please see the transcript for details of the committee discussion.*

The meeting was adjourned at approximately 12:27 p.m.