

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

**Final 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 15, 2022**

Location: Please note that due to the impact of this COVID-19 pandemic, all meeting participants will be joining this advisory committee meeting via an online teleconferencing platform

Topic: The committees discussed new drug application (NDA) 213231, for tramadol hydrochloride injection, submitted by Avenue Therapeutics, Inc., for the management of moderate to moderately severe pain in adults in a medically supervised healthcare setting. The issues for the committees to discuss include the clinical relevance of tramadol hydrochloride injection, an opioid intended for management of acute pain in a medically supervised healthcare setting, when its onset of action is delayed, and its proposed dosing is a fixed-dosing regimen.

These summary minutes for the February 15, 2022 joint meeting of 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 were approved on March 4, 2022.

I certify that I attended the February 15, 2022 joint meeting of the AADPAC and DSaRM 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/
Brian T. Bateman, MD
Chairperson, AADPAC

**Final Summary Minutes of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee Joint Meeting
February 15, 2022**

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 jointly on February 15, 2022. The meeting presentations were heard, viewed, captioned, and recorded through an online teleconferencing platform. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Avenue Therapeutics, Inc. The meeting was called to order by Brian T. Bateman, MD, MSc (Chairperson). The conflict of interest statement was read into the record by Moon Hee V. Choi, PharmD (Designated Federal Officer). There were approximately 246 people online. There were a total of nine Open Public Hearing (OPH) speaker presentations.

A verbatim transcript will be available, in most instances, at approximately ten to twelve weeks following the meeting date.

Agenda:

The committees discussed new drug application (NDA) 213231, for tramadol hydrochloride injection, submitted by Avenue Therapeutics, Inc., for the management of moderate to moderately severe pain in adults in a medically supervised healthcare setting. The issues that the committees discussed include the clinical relevance of tramadol hydrochloride injection, an opioid intended for management of acute pain in a medically supervised healthcare setting, when its onset of action is delayed, and its proposed dosing is a fixed-dosing regimen.

Attendance:

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

Brian T. Bateman, MD, MSc (*Chairperson*); Basavana G. Goudra, MD, FRCA, FCARSCI; Jennifer Higgins, PhD (*Consumer Representative*); Maryam Jowza, MD; Maura S. McAuliffe, CRNA, MSN, MSNA, PhD, FAAN; Mary Ellen McCann, MD, MPH; Rebecca Richmond, PharmD, BCPS; Abigail B. Shoben, PhD; Michael Sprintz, DO, DFASAM; Sherif Zaafran, MD, FASA

Anesthetic and Analgesic Drug Products Advisory Committee Member Not Present (Voting): Richard D. Urman, MD, MBA

Anesthetic and Analgesic Drug Products Advisory Committee Member Present (Non-Voting): Jay Horrow, MD, MS, FACC (*Industry Representative*)

Drug Safety and Risk Management Advisory Committee Members Present (Voting):

Karim Anton Calis, PharmD, MPH, FASHP, FCCP; Marie R. Griffin, MD, MPH; Sonia Hernandez-Diaz, MD, MPH, DrPH; John B. Hertig, PharmD, MS, CPPS, FASHP; Collin A.

February 15, 2022

Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee

Hovinga, PharmD, MS, FCCP; Krista F. Huybrechts, MS, PhD; Vincent Lo Re III, MD, MSCE; Mara McAdams DeMarco, MS, PhD; Suzanne B. Robotti (*Consumer Representative*)

Drug Safety and Risk Management Advisory Committee Members Not Present (Voting):
Martin Kulldorff, PhD; Lewis S. Nelson, MD

Drug Safety and Risk Management Advisory Committee Member Present (Non-Voting):
Reema J. Mehta, PharmD, MPH (*Industry Representative*)

Temporary Members (Voting): Joseph O'Brien, MBA (*Patient Representative*); Anne-Michelle Ruha, MD; Kevin L. Zacharoff, MD, FACIP, FACPE, FAAP

FDA Participants (Non-Voting): Rigoberto Roca, MD; Lisa Wiltrout, MD; Judy A. Staffa, PhD; Tamra Meyer, PhD, MPH; Dominic Chiapperino, PhD

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

Open Public Hearing Speakers Present: Primarius Andreas Faltlhauser, MD, DEAA, JFICM, FCCA; Sidney M. Wolfe, MD (Public Citizen); Richard A. Pollak, DPM, MS; C. Aaron Dees; Clint Matthews; Diana Zuckerman, PhD (National Center for Health Research); David Leiman, MD, MBA; Jim Baccus; Adriane Fugh-Berman, MD (PharmedOut)

The agenda was as follows:

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| Call to Order | Brian T. Bateman, MD, MSc Chairperson, AADPAC |
| Introduction of Committee and Conflict of Interest Statement | Moon Hee V. Choi, PharmD Designated Federal Officer, AADPAC |
| Statement on Formal Dispute Resolution Request | Moon Hee V. Choi, PharmD |
| FDA Opening Remarks | Rigoberto Roca, MD Director Division of Anesthesiology, Addiction Medicine and Pain Medicine (DAAP), Office of Neuroscience (ON) Office of New Drugs (OND), CDER, FDA |
| APPLICANT PRESENTATIONS | Avenue Therapeutics, Inc. |
| Introduction | Lucy Lu, MD President and CEO Avenue Therapeutics, Inc. |
| Mechanism of Action and Intravenous (IV) Tramadol Experience in European Union | Prof. Richard Langford, MD Lead Consultant Pain Service, The London Clinic |

February 15, 2022

Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee

APPLICANT PRESENTATIONS (CONT.)

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| Pharmacokinetics, Clinical Efficacy, and Safety | Lucy Lu, MD |
| Discussion of FDA Concerns | Lucy Lu, MD |
| Epidemiology of Abuse of Tramadol | Janetta Iwanicki, MD Chief Scientific Officer Rocky Mountain Poison and Drug Safety |
| Clinical Perspective from a U.S. Investigator | Harold Minkowitz, MD Adjunct Associate Professor Anesthesiology and Perioperative Medicine MD Anderson Cancer Center |
| Clarifying Questions for Applicant | |

BREAK

FDA PRESENTATIONS

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| Tramadol IV: A Multidisciplinary Review | Lisa Wilttrout, MD Medical Officer DAAP, ON, OND, CDER, FDA |
| Abuse Potential Considerations for Tramadol IV Injection Under NDA 213231 | James M. Tolliver, PhD Senior Pharmacologist Controlled Substance Staff, CDER, FDA |
| Epidemiologic Data and Public Health Considerations in Evaluating Benefit-Risk of IV Tramadol | Christina R. Greene, PhD Senior Epidemiologist, Division of Epidemiology II Office of Pharmacovigilance and Epidemiology Office of Surveillance and Epidemiology, CDER, FDA |
| Clarifying Questions for FDA | |

LUNCH

OPEN PUBLIC HEARING

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|---|---------------------------|
| Charge to the Committee | Rigoberto Roca, MD |
| Questions to the Committee/Committee Discussion | |

BREAK

Questions to the Committee/Committee Discussion (cont.)

ADJOURNMENT

Questions to the Committees:

1. **DISCUSSION:** Discuss the importance of time to onset of action and risks related to delayed onset of action for intravenous tramadol proposed for the management of moderate to severe acute pain in the inpatient setting, such as post-operative or acute severe injury setting.

Committee Discussion: The committee members expressed varying levels of concern regarding the risks related to the delayed onset of action for intravenous (IV) tramadol. Some committee members were not concerned about the time to onset of action for this drug product, noting the distinction in treatment setting to be important as patients are closely monitored in the inpatient setting (whereas they would have concern about the delayed onset resulting in safety issues for patients treated in an Emergency Department (ED) or Ambulatory Surgical Care (ASC) setting, who are discharged shortly after treatment). One member noted it would be helpful, if this drug product were approved, to have criteria on how long a patient treated in the ED or ASC setting needs to be monitored before being discharged. Some members suggested that in skillful hands, IV tramadol could be given early and the delayed onset could be leveraged as part of an effective plan to manage analgesia in the post-operative/inpatient setting, although one member noted it may not be handled optimally in a real world setting.

Many other committee members expressed that the delayed onset of IV tramadol was problematic and pointed out that clear labeling and extensive education on the delayed onset of this drug product would be needed. Some members voiced concern about the proposed use of NSAIDs as rescue medication after starting with IV tramadol – the result being use of opioids in patients who don't necessarily require it. Regarding the potential for opioid stacking and its associated safety risks due to IV tramadol's delayed onset of action, some members acknowledged that it is a theoretical concern while others were less concerned due to the proposed use in a controlled inpatient setting. Some members pointed out that the trials presented did not provide any insight into the safety of opioid stacking as opioids were not allowed as a rescue medication in the studies. A few members were reassured by the European pharmacovigilance data presented while others noted that scheduling and use of opioids are different in Europe than in the United States, and more real world data specifically examining opioid stacking with IV tramadol is warranted. Please see the transcript for details of the Committees' discussion.

2. **DISCUSSION:** Discuss the benefits and risks of intravenous tramadol for acute pain management in the inpatient setting considering its mechanism of analgesia, drug pharmacokinetics, and complex metabolism.

Committee Discussion: One committee member acknowledged that the safety risk associated with opioid stacking was a theoretical risk but without significant adverse events observed in other countries where it is approved, and noted that it would be advantageous to have a Schedule IV opioid as a treatment option. Another member commented that the studies presented could have been more useful if an active comparator such as ibuprofen were used instead of placebo and echoed previous comments about safety data on IV tramadol from

Europe not being comparable to the United States population. The Committee acknowledged that much of the benefits and risks of IV tramadol for acute pain management in the inpatient setting had already been addressed in question #1. Please see the transcript for details of the Committees' discussion.

3. **DISCUSSION:** Discuss the relevance of tramadol's abuse potential as a Schedule IV substance in the context of the proposed use for the management of acute pain in an inpatient setting with consideration of the following issues:
 - a. Any impact on a patient's subsequent risk of abuse, misuse, or development of opioid use disorder in the outpatient setting.

***Committee Discussion:** With regard to IV tramadol's abuse potential as a Schedule IV substance on a patient's subsequent risk of abuse, misuse or development of opioid use disorder (OUD) in the outpatient setting, one member noted the potential of a drug scheduled to be delivered every 4 to 6 hours (instead of when needed) leading to the theoretical risk of patients getting a dose of an analgesic they don't need, contributing to the potential risk of abuse. Another member mentioned the potential for a false sense of safety with a Schedule IV substance, leading to more opioids being prescribed. One committee member highlighted the Applicant's data demonstrating less euphoria associated with this drug product, concluding that IV tramadol likely has less potential for abuse or misuse. Several members agreed on the increased likelihood of patients being sent home or discharged on oral tramadol after being given IV tramadol in the inpatient setting, leading to an increase in abuse of tramadol and side effects. While one member noted this may be a benefit due to lower abuse potential (versus discharging a patient on a Schedule II narcotic), another member highlighted the concern of an increase in drug interactions with more prescribing of oral tramadol resulting in seizures, serotonin syndrome, etc. One member pointed out there are currently few options available for weaker narcotics and preventing use of IV tramadol because of theoretical safety concerns may result in patients getting a stronger narcotic than needed. Please see the transcript for details of the Committees' discussion.*

- b. Any comparative advantage over currently available Schedule II intravenous opioids approved for the management of acute pain in an inpatient setting.

***Committee Discussion:** The Committee members expressed varying views on IV tramadol's abuse potential as a Schedule IV substance and any comparative advantage over Schedule II opioids. Several members commented that there was no evidence presented demonstrating that IV tramadol use in a medically supervised setting will result in less misuse or abuse after discharge when compared to the use of a Schedule II opioid in the same setting. One member noted that due to IV tramadol's delayed onset, it is expected to be used frequently in combination with Schedule II opioids and it is unclear what advantage there is to administer IV tramadol over just starting with a Schedule II analgesic. Another member noted that if IV tramadol is able to produce adequate pain relief, it has the possible advantage of clinicians being able to avoid*

February 15, 2022

Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee

sending a patient home with a Schedule II drug. Please see the transcript for details of the Committees' discussion.

4. **VOTE:** Has the Applicant submitted adequate information to support the position that the benefits of their product outweigh the risks for the management of acute pain severe enough to require an opioid analgesic in an inpatient setting?
 - a. If you voted 'Yes', please discuss the rationale for your vote and specify whether any post-approval studies should be required.
 - b. If you voted 'No', please discuss the rationale for your vote and what additional data are needed for approval.

Vote Result: Yes: 8 No: 14 Abstain: 0

Committee Discussion: *A majority of members voted "No," agreeing that the Applicant did not submit adequate information to support the position that the benefits for their product outweigh the risks for the management of acute pain severe enough to require an opioid analgesic in an inpatient setting. These members were in agreement that strong evidence of IV tramadol's benefit was not demonstrated, with many citing the use of placebo in the studies presented and calling for additional data comparing IV tramadol against a Schedule II opioid or non-opioid analgesic. Several members also noted the need for future trials to be conducted in an inpatient setting as proposed by the labeling. Many members were also in agreement about the safety concerns for this product, citing the delayed onset of action leading to potential for adverse events due to opioid stacking, the inability to titrate the dosing, the unpredictability of the drug's pharmacokinetics, and the drug's potential for interactions with other medications. The members who voted "No" were in agreement that more data was needed to assess IV tramadol's overall safety, with some members noting a specific need for more real world data on safety after patients are discharged from a medically supervised setting.*

Those who voted "Yes" agreed that IV tramadol's efficacy was demonstrated by the pivotal trials, with several emphasizing the need for proper use of this drug product in an inpatient medically supervised setting to mitigate potential safety concerns regarding opioid stacking. One member noted the current lack of a Schedule IV intravenous opioid available as a treatment option. Several members noted the need for proper education, clear labeling for use, and appropriate guidance on monitoring time prior to discharge as strategies to mitigate the safety risks of this drug product. One member also suggested a need for post approval tracking on how IV tramadol affects different ethnic groups, noting differences in diversity between the populations of the United States and Europe. Please see the transcript for details of the Committees' discussion.

The meeting was adjourned at approximately 5:36 p.m. ET.