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 January 15, 2020

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

Topic: During the morning session, the committees discussed new drug application (NDA) 213426, for tramadol 44 milligrams (mg) and celecoxib 56 mg tablet, which contains a fixed-dose combination of an opioid and a non-steroid anti-inflammatory drug, submitted by Esteve Pharmaceuticals, S.A., for the management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate. The committees were asked to discuss the safety and efficacy data as well as the overall risk-benefit profile of the product.

During the afternoon session, the committees discussed NDA 209653, for an extended-release oral tablet formulation of oxycodone, submitted by Intellipharmaceutics Corp., with the management of moderate-to-severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. The product has been formulated with properties intended to deter abuse, and the applicant has submitted data to support these abuse-deterrent properties for this product. The committees were asked to discuss whether the applicant has demonstrated abuse-deterrent properties for their product that would support labeling, as well as to discuss the overall risk-benefit profile of the product.

These summary minutes for the January 15, 2020 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 March 3, 2020.

I certify that I attended the January 15, 2020 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 and that these minutes accurately reflect what transpired.

/s/	**/s/**
Moon Hee V. Choi, PharmD	Ronald S. Litman, DO, ML
Designated Federal Officer, AADPAC	Chairperson, AADPAC

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
January 15, 2020

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 January 15, 2020, 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, Esteve Pharmaceuticals, S.A., and Intellipharmaceutics Corp. The meeting was called to order by Ronald S. Litman, DO, ML (Chairperson). The conflict of interest statement was read into the record by Moon Hee V. Choi, PharmD (Designated Federal Officer). There were approximately 125 people in attendance during the morning session and approximately 115 people in attendance during the afternoon session. There were six Open Public Hearing (OPH) presentations during the morning session and one OPH presentation during the afternoon session.

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

Agenda:

During the morning session, the committees discussed new drug application (NDA) 213426, for tramadol 44 milligrams (mg) and celecoxib 56 mg tablet, which contains a fixed-dose combination of an opioid and a non-steroid anti-inflammatory drug, submitted by Esteve Pharmaceuticals, S.A., for the management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate. The committees were asked to discuss the safety and efficacy data as well as the overall risk-benefit profile of the product.

During the afternoon session, the committees discussed NDA 209653, for an extended-release oral tablet formulation of oxycodone, submitted by Intellipharmaceutics Corp., with the management of moderate-to-severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. The product has been formulated with properties intended to deter abuse, and the applicant has submitted data to support these abuse-deterrent properties for this product. The committees were asked to discuss whether the applicant has demonstrated abuse-deterrent properties for their product that would support labeling, as well as to discuss the overall risk-benefit profile of the product.

Attendance:

Anesthetic and Analgesic Drug Products Advisory Committee Members Present (Voting): Basavana G. Goudra, MD, FRCA, FCARSCI; Jennifer Higgins, PhD (Consumer Representative)**;** Ronald S. Litman, DO, ML (Chairperson); Maura S. McAuliffe, CRNA, MSN,

MSNA, PhD, FAAN; Mary Ellen McCann, MD, MPH; Abigail B. Shoben, PhD; Kevin L. Zacharoff, MD, FACIP, FACPE, FAAP; Lonnie Zeltzer, MD
Drug Safety and Risk Management Advisory Committee Members Present (Voting): Sonia Hernandez-Diaz, MD, MPH, DrPH; Steven B. Meisel, PharmD, CPPS; Suzanne B. Robotti (Consumer Representative); Soko Setoguchi, MD, DrPh

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 Member Present (Non-Voting): Reema J. Mehta, PharmD, MPH (Industry Representative)

Anesthetic and Analgesic Drug Products Advisory Committee Members Not Present (Voting): Maryam Jowza, MD; Michael Sprintz, DO, DFASAM; Richard D. Urman, MD, MBA

Drug Safety and Risk Management Advisory Committee Members Not Present (Voting): Denise M. Boudreau, PhD, RPh; Karim Anton Calis, PharmD, MPH, FASHP, FCCP; Marie R. Griffin, MD, MPH; Laurel A. Habel, MPH, PhD; Martin Kulldorff, PhD; Anne-Michelle Ruha, MD, FACMT; Terri L. Warholak, PhD, RPh, CPHQ, FAPhA

Temporary Members (Voting): Maryann E. Amirshahi, PharmD, MD, MPH, PhD; Laura Block, PharmD, EMT-B (Patient Representative); Martin Garcia-Bunuel, MD; Traci C. Green, PhD, MSc; Lee D. Hoffer, PhD, MPE; Brandon D.L. Marshall, PhD; Edward Michna, MD, JD, RPh; Marjorie Shaw Phillips, MS, RPh, FASHP, CIP; Paul Pisarik, MD, MPH; Friedhelm Sandbrink, MD; Maria E. Suarez-Almazor, MD, PhD; Patrick Sullivan, DVM, PhD; Linda S. Tyler, PharmD; Sherif Zaafran, MD, FASA

FDA Participants (Non-Voting): Rigoberto Roca, MD; Judy Staffa, PhD, RPh; Naomi Lowy, MD; Dominic Chiapperino, PhD; (morning session only); Pamela Horn, MD (morning session only); James Tolliver, PhD (afternoon session only); Elizabeth Kilgore, MD, MS (afternoon session only).

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

Open Public Hearing Speakers Present: ***Morning Session*** – Nina Zeldes, MSc (National Center for Health Research); Ira J. Gottlieb (Chesapeake Research Group); Jody L. Green, PhD, FAACT, CCRP (Inflexxion, an IBH Company); John J. Coleman, MA, MS, PhD; Edd Lyon, MD; Adriane Fugh-Berman MD (Physicians for Rational Opioid Prescribing and Pharmed Out, Georgetown Univ. Medical Center); ***Afternoon Session*** – Nina Zeldes, MSc (National Center for Health Research)

The morning session agenda was as follows:

Call to Order and Introduction of Committee	**Ronald S. Litman, DO, ML** Chairperson, AADPAC

Conflict of Interest Statement	**Moon Hee V. Choi, PharmD** Designated Federal Officer, AADPAC
FDA Opening Remarks	**Naomi Lowy, MD** Deputy Director (Acting) Division of Anesthesiology, Addiction Medicine and Pain Medicine (DAAP) Office of Neuroscience (ON) Office of New Drugs, CDER, FDA
APPLICANT PRESENTATIONS	**Esteve Pharmaceuticals S.A.**
Introduction	**Mark Mayhew, PhD** Director, CTC Program Esteve Pharmaceuticals, S.A.
Urgent Need in Opioid Analgesia	**Eugene R. Viscusi, MD** Professor of Anesthesiology Chief of Pain Medicine Director, Acute Pain Management Thomas Jefferson University Philadelphia, PA
Phase I Clinical Pharmacology Phase 2 Dose-Finding Study	**Carlos R. Plata-Salaman, DSc, MD** Chief Scientific Officer and Chief Medical Officer Esteve Pharmaceuticals, S.A.
Phase 3 Efficacy and Safety	**Neus Gascon, MD** Head of Medical Sciences Esteve Pharmaceuticals, S.A.
Benefit-Risk Assessment	**Oscar de Leon-Casasola, MD** Chief, Division of Pain Medicine Professor of Oncology Roswell Park Cancer Institute Professor of Anesthesiology and Medicine The Jacobs School of Medicine at The University of Buffalo
Clarifying Questions	
FDA PRESENTATION	
Review of Recent Data on Use, Misuse, Abuse, and Overdose of Tramadol and Comparator Opioid Analgesics	**Saranrat Wittayanukorn, PhD** Epidemiologist, Division of Epidemiology II Office of Pharmacovigilance and Epidemiology Office of Surveillance and Epidemiology (OSE) CDER, FDA

Clarifying Questions	
BREAK	
OPEN PUBLIC HEARING	
Charge to the Committee	**Naomi Lowy, MD**
Questions to the Committee/ Committee Discussion	
LUNCH	

The afternoon session agenda was as follows:

Call to Order and Introduction of Committee	**Ronald S. Litman, DO, ML** Chairperson, AADPAC
Conflict of Interest Statement	**Moon Hee V. Choi, PharmD** Designated Federal Officer, AADPAC
FDA Opening Remarks	**Rigoberto A. Roca, MD** Director (Acting) Division of Anesthesiology, Addiction Medicine and Pain Medicine (DAAP) Office of Neuroscience (ON) Office of New Drugs, CDER, FDA
APPLICANT PRESENTATIONS	**Intellipharmaceutics Corp.**
Introduction	**Isa Odidi, MBA, PhD, DSc.** Chairman, CEO, co-CSO, co-Founder Intellipharmaceutics Corp.
Abuse-Deterrance (Category 1) Studies and Nonclinical Excipient Safety Studies	**Olu Aloba, RPh, PhD, RAC** Senior Director, CMC Services Camargo Pharmaceutical Services
APPLICANT PRESENTATIONS (CONT.)	
Clinical Pharmacology and Abuse-Deterrence (Human Abuse Potential) Studies	**Ruth Stevens, PhD, MBA** Chief Scientific Officer, Exec VP Camargo Pharmaceutical Services
Risk/Benefit Profile and Risk Mitigation Plans	**Isa Odidi, MBA, PhD, DSc.**
Clarifying Questions	

FDA PRESENTATIONS

Use, Misuse, Abuse and Deaths involving Oxycodone and Other Opioids in the United States	**Matthew Daubresse, MHS, DrPH (candidate)** Epidemiologist, Drug Abuse Division of Epidemiology II Office of Pharmacovigilance and Epidemiology OSE, CDER, FDA
Nonclinical Safety Assessment of Aximris XR Excipients	**Jaime D'Agostino, PhD** Pharmacology/Toxicology Reviewer Division of Pharmacology/Toxicology for Neuroscience, ON, OND, CDER, FDA
Agency Interpretation of In Vitro and Human Abuse Potential Studies	**James Tolliver, PhD** Pharmacologist Controlled Substance Staff Office of the Center Director, CDER, FDA
Clinical Summary – Aximris XR	**Elizabeth Kilgore, MD, MS** Medical Officer DAAP, ON, OND, CDER, FDA
Clarifying Questions	

OPEN PUBLIC HEARING

BREAK

Charge to the Committee	**Rigoberto Roca, MD**
Questions to the Committee/Committee Discussion	

ADJOURNMENT

Questions to the Committees:

MORNING SESSION:

1. **DISCUSSION:** Considering the abuse potential of tramadol 44mg and celecoxib 56mg tablets and its proposed use for the management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate, please discuss any concerns you have regarding the impact of this product, if approved, on public health.

   Committee Discussion: *In considering the abuse potential of tramadol 44mg and celecoxib 56mg tablets and its proposed use, some Committee members had concerns regarding the impact of this product on public health (if approved) and expressed the need for comparison data of the combination product to its individual ingredients at therapeutic doses and more*

specifically, comparison data to celecoxib alone. These Committee members added that the efficacy of this combination product for 12 hours could be due to the effects of celecoxib, and thus there would be no benefit of introducing another opioid option in terms of public health. Other Committee members noted the lack of flexibility for titration in a fixed dose combination product, lack of data on the risks of intravenous abuse of the formulation, which is a co-crystal, concerns about the toxicity of celecoxib if abused by the intravenous route, and the financial considerations of the combination product compared to the currently approved generic options of each ingredient. Those Committee members who did not express concerns regarding the public health impact stated that both individual ingredients have already been shown to have favorable profiles and thus agreed that this combination product of tramadol 44mg and celecoxib 56mg tablets could be, if approved, a better alternative to what is currently available to treat acute pain in terms of public health. Other Committee members agreed and used the term "tramadol light" for the benefits of tramadol observed in the relatively low dose of tramadol in the combination product compared to other available tramadol products while having demonstrated efficacy and thus, the possibility of less abuse in terms of public health. Please see the transcript for details of the Committees' discussion.

2. **DISCUSSION:** Discuss whether the benefits outweigh the risks for the proposed indication. Discuss if any additional data are needed for this application to be approved.

   Committee Discussion: *Several Committee members who agreed that the benefits of tramadol 44mg and celecoxib 56mg tablets outweighed the risks for the proposed indication expressed that tramadol and celecoxib have been individually available for a long time and thus, combining the two ingredients as a lower-dose combination product would make available an alternative to opioid treatments currently used for acute pain. These Committee members also noted that this combination product may decrease the use of opioid rescue medications and noted the convenience of using fewer pills. The Committee members who disagreed that the benefits outweigh the risks for the proposed indication argued that the combination product is not effective and patients will need some type of rescue pain medication, thus increasing the potential of adding on another, stronger opioid. Other Committee members added that combination tablets decrease flexibility in titrating doses and the potential issues involved in using the combination tablet once pain is less severe and an opioid is no longer needed. Please see the transcript for details of the Committees' discussion.*

3. **VOTE:** Do you recommend approval of tramadol 44mg and celecoxib 56mg tablets for the proposed indication of the management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate?

   Vote Result: Yes: 13 No: 13 Abstain: 0

   Committee Discussion*: The Committee members were split on whether they recommend approval of tramadol 44mg and celecoxib 56mg tablets for the proposed indication of the management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate. The majority of those who voted "Yes"*

indicated that the overall benefits outweigh the risks for the proposed indication. These committee members noted that efficacy was demonstrated in the Phase 3 study and the pharmacokinetic data suggested an efficacy and safety advantage over tramadol and celecoxib when used individually. Other Committee members who were in favor of approval noted the potential advantages of the co-crystal feature of tramadol, a schedule IV controlled substance, and celecoxib, as it may replace use of some short-acting, Schedule II opioids. The Committee members who voted "No" stated the benefit/risk profile was not favorable and noted the lack of comparative data of the combination product to its single ingredients. Some of these Committee members voiced concerns that the perception of tramadol 44mg and celecoxib 56mg tablets being safer may lead to over-prescribing, abuse/misuse and potential for downstream effects. Please see the transcript for details of the Committees' discussion.

AFTERNOON SESSION:

1. **DISCUSSION:** Please discuss whether the Applicant has demonstrated that AXIMRIS XR (oxycodone extended-release tablets) has properties that can be expected to deter abuse by the following routes:

   - Intravenous

     Committee Discussion: *The Committee members agreed that the Applicant demonstrated that AXIMRIS XR (oxycodone extended-release tablets) has properties that can be expected to deter abuse by the intravenous route. One Committee member added that the extractability of AXIMRIS XR was much lower compared to OxyContin, which has abuse-deterrent properties for the intravenous route. Please see the transcript for details of the Committees' discussion.*

   - Intranasal

     Committee Discussion: *The Committee members agreed that the Applicant did not demonstrate that AXIMRIS XR (oxycodone extended-release tablets) has properties that can be expected to deter abuse by the intranasal route. One Committee member added that AXIMRIS XR was more easily manipulated under certain conditions compared to OxyContin, and thus would more likely be abused via the intranasal route. One Committee member added that AXIMRIS XR may be more favorable for intranasal use compared to Oxycontin based on the pharmacokinetic comparison data from the intranasal human abuse potential study. Committee members also questioned the lack of pharmacokinetic/pharmacodynamic (PK/PD) correlation for the study. Please see the transcript for details of the Committees' discussion.*

   - Oral

     Committee Discussion: *The Committee members agreed that the Applicant did not demonstrate that AXIMRIS XR (oxycodone extended-release tablets) has properties that can be expected to deter abuse by the oral route. Some Committee members agreed that*

in general, the term abuse-deterrent and the associated requirements for labelling need to be more clearly defined by the Agency. Please see the transcript for details of the Committees' discussion.

2. **DISCUSSION:** The Applicant is requesting approval of AXIMRIS XR as an analgesic with properties expected to deter abuse by the intravenous route. Discuss the implications of approval of AXIMRIS XR that can be expected to deter abuse by a single route.

   Committee Discussion: *Overall, the Committee members agreed and expressed that it was difficult to approve a product and label it to have "abuse-deterrent" properties if it can only deter abuse via a single route. The Committee members also agreed that if a product has abuse-deterrent properties for one route of administration, the product will potentially be abused via the other routes. One Committee member stated that the ideal would be to label a product to have abuse-deterrence via all routes but acknowledged that it would be difficult to develop such a product for approval. Several Committee members noted that although AXIMRIS XR demonstrated properties expected to deter abuse by the intravenous route, intravenous abuse is the least common form of abuse. They expressed more concern for the potential to abuse via the intranasal route and agreed that it would be more ideal for AXIMRIS XR to have abuse deterrent properties to deter abuse via the intranasal route as well as the intravenous route. Please see the transcript for details of the Committees' discussion.*

3. **DISCUSSION:** Discuss whether you have any concerns regarding the impact of AXIMRIS XR on public health. Take into consideration its potential effect on abuse of extended-release oxycodone as well as potential consequences of administration of this product by unintended routes.

   Committee Discussion: *Since AXIMRIS XR deters abuse through the intravenous route only, it was noted that this drug product may push abusers to abuse through the intranasal route. Thus, if approved, AXIMRIS XR may have a negative impact on public health. Please see the transcript for details of the Committees' discussion.*

4. **DISCUSSION:** Discuss whether the benefits outweigh the risks for the proposed indication. Discuss if any additional data are needed for this application to be approved.

   Committee Discussion: *Overall, the Committee members agreed that the benefits do not outweigh the risks for the proposed indication. The Committee members noted that AXIMRIS XR is similar to what is currently available on the market; furthermore, it did not show abuse-deterrent advantages to what is currently available as it has properties to deter abuse via the intravenous route only. In terms of additional data needed, some Committee members suggested that data on the effects of taking more than the intended amount of the product would be helpful. One Committee member noted that the Applicant needs to clarify the pharmacokinetic data in the insufflation study to explain the disconnect of high* C_{max} *concentrations without having a significant impact on Drug Liking or Take Drug Again parameters. Please see the transcript for details of the Committees' discussion.*

5. **VOTE:** Do you recommend approval of AXIMRIS XR (oxycodone extended-release tablets) for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate?

   Vote Result: Yes: 2 No: 24 Abstain: 0

   ***Committee Discussion**: A vast majority of the Committee members voted "No", indicating that they did not recommend approval of AXIMRIS XR (oxycodone extended-release tablets) for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. These Committee members agreed that AXIMRIS XR did not offer any abuse-deterrent advantages to what is currently available on the market and added that it offered more disadvantages such as the issues involving abuse via the intranasal route. Moreover, committee members expressed concerns that experienced opioid users may abuse higher strength or multiple tablets via the intranasal route in the real world, which may result in higher plasma level and pose higher risks of overdose. The two Committee members who voted "Yes" stated the question being asked is a question on approvability of the product and not abuse-deterrent properties. Please see the transcript for details of the Committees' discussion.*

The meeting was adjourned at approximately 5:05 p.m. on January 15, 2020.