CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

208090Orig1s004

Trade Name: XTAMPZA ER®

Generic or Proper Name: oxycodone

Sponsor: Collegium Pharmaceutical, Inc.

Approval Date: 11/06/2017

Indication: XTAMPZA ER® is An opioid agonist indicated for the management of pain severe enough to require daily, around-the-clock, long-term opiod treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve XTAMPZA ER for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.
- XTAMPZA ER is not indicated as an as-needed (prn) analgesic.

CENTER FOR DRUG EVALUATION AND RESEARCH

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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208090/S-004

SUPPLEMENT APPROVAL

Collegium Pharmaceutical Inc
780 Dedham St, Suite 800
Canton, MA 02021

Attention: John F. Weet, PhD
Vice President, Regulatory Affairs and Quality Assurance

Dear Dr. Weet:

Please refer to your Supplemental New Drug Application (sNDA) dated and received October 4, 2016, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for XTAMPZA ER (oxycodone) extended-release capsules.

We acknowledge receipt of your major amendment dated March 24, 2017, which extended the goal date by three months.

This Prior Approval supplemental new drug application proposes changes to the abuse-deterrent language in the DRUG ABUSE AND DEPENDENCE section of the product label.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, Medication Guide), with the addition of any labeling changes in pending "Changes Being

Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription

Drug Promotion (OPDP),
see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Selma Kraft, Regulatory Project Manager, at (240)-402-9700.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, MD
Director
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHARON H HERTZ
11/06/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use XTAMPZA® ER safely and effectively. See full prescribing information for XTAMPZA ER.

XTAMPZA ER (oxycodone) extended-release capsules, for oral use, CII
Initial U.S. Approval: 1950

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

See full prescribing information for complete boxed warning.

- **XTAMPZA ER exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk before prescribing and monitor regularly for development of these behaviors and conditions. (5.1)**
- **Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. (5.2)**
- **Accidental ingestion of XTAMPZA ER, especially by children, can result in fatal overdose of oxycodone. (5.2)**
- **Prolonged maternal use of XTAMPZA ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.3)**
- **Concomitant use with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in a fatal overdose of oxycodone from XTAMPZA ER. (5.4, 12.3)**
- **Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation. (5.5, 7)**

----------RECENT MAJOR CHANGES----------

Boxed Warning	12/2016
Warnings and Precautions, Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants (5.5)	12/2016

INDICATIONS AND USAGE

XTAMPZA ER is an opioid agonist indicated 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. (1)

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve XTAMPZA ER for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. (1)
- XTAMPZA ER is not indicated as an as-needed (prn) analgesic. (1)

DOSAGE AND ADMINISTRATION

- XTAMPZA ER at a total daily dose greater than 72 mg (equivalent to 80 mg oxycodone hydrochloride [HCl]) or a single dose greater than 36 mg (equivalent to 40 mg oxycodone HCl) is only for use in patients in whom tolerance to an opioid of comparable potency has been established. (2.1)
- Patients considered opioid tolerant are those receiving, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl
- Instruct patients to take XTAMPZA ER capsules with food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, XTAMPZA ER can also be taken by sprinkling the capsule contents on soft foods or into a cup and then administering directly into the mouth, or through a gastrostomy or nasogastric feeding tube. (2.6)

DOSAGE FORMS AND STRENGTHS

- Extended-release capsules:
  - 9 mg (equivalent to 10 mg oxycodone HCl)
  - 13.5 mg (equivalent to 15 mg oxycodone HCl)
  - 18 mg (equivalent to 20 mg oxycodone HCl)
  - 27 mg (equivalent to 30 mg oxycodone HCl)
  - 36 mg (equivalent to 40 mg oxycodone HCl). (3)

CONTRAINDICATIONS

- Significant respiratory depression (4)
- Acute or severe bronchial asthma (4)
- Known or suspected gastrointestinal obstruction, including paralytic ileus (4)
- Hypersensitivity to oxycodone (4)

WARNINGS AND PRECAUTIONS

- Risk of life-threatening respiratory depression in patients with chronic pulmonary disease or in elderly, cachectic, or debilitated patients: Monitor closely, particularly during initiation and titration. (5.6)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.7)
- Severe hypotension: Monitor during dosage initiation and titration. Avoid use of XTAMPZA ER in patients with circulatory shock (5.8)
- Risks of use in patients with increased intracranial pressure, brain tumors, head injury, or impaired consciousness: Monitor for sedation and respiratory depression. Avoid use of XTAMPZA ER in patients with impaired consciousness or coma. (5.9)

ADVERSE REACTIONS

Most common adverse reactions (>5%) were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Collegium Pharmaceutical, Inc. at 1-855-331-5615 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Interactions with CNS depressants: Concomitant use may cause profound sedation, respiratory depression, coma, and death. If coadministration is required, consider dose reduction of one or both drugs because of additive pharmacological effects and monitor closely. (5.5, 7)
- Serotonergic Drugs: Concomitant use may result in serotonin syndrome. Discontinue XTAMPZA ER if serotonin syndrome is suspected. (7)
- Mixed agonist/antagonist and partial agonist opioid analgesics: Avoid use with XTAMPZA ER because they may reduce analgesic effect of XTAMPZA ER or precipitate withdrawal symptoms. (7)
- Monoamine Oxidase Inhibitors (MAOIs): Can potentiate the effects of oxycodone. Avoid concomitant use in patients receiving MAOIs or within 14 days of stopping treatment with an MAOI. (7)

USE IN SPECIFIC POPULATIONS

- Pregnancy: May cause fetal harm. (8.1)
- Lactation: Not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2017

per hour, 30 mg oral oxycodone HCl per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid. (2.1)

- Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (2.1)
- For opioid-naïve and opioid non-tolerant patients, initiate with 9 mg (equivalent to 10 mg oxycodone HCl) capsules orally every 12 hours with food. (2.2)
- The daily dose of XTAMPZA ER must be limited to a maximum of 288 mg per day (equivalent to 320 mg oxycodone HCl per day) (2.1)
- Hepatic impairment: Initiate therapy at 1/3 to 1/2 the usual dosage and titrate carefully. Monitor carefully. Use alternate analgesia for patients requiring less than 9 mg. (2.3, 8.6)
- Do not abruptly discontinue XTAMPZA ER in a physically dependent patient. (2.5)

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse, and Misuse

XTAMPZA ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing XTAMPZA ER and monitor all patients regularly for the development of these behaviors or conditions *[see Warnings and Precautions (5.1)]*.

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of XTAMPZA ER. Monitor for respiratory depression, especially during initiation of XTAMPZA ER or following a dose increase *[see Warnings and Precautions (5.2)]*.

Accidental Ingestion

Accidental ingestion of even one dose of XTAMPZA ER, especially by children, can result in a fatal overdose of oxycodone *[see Warnings and Precautions (5.2)]*.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of XTAMPZA ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Warnings and Precautions (5.3)]*.

Cytochrome P450 3A4 Interaction

The concomitant use of XTAMPZA ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving XTAMPZA ER and any CYP3A4 inhibitor or inducer *[see Warnings and Precautions (5.4) and Clinical Pharmacology (12.3)]*.

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death *[see Warnings and Precautions (5.5), Drug Interactions (7)]*.

- **Reserve concomitant prescribing of XTAMPZA ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

1 INDICATIONS AND USAGE

XTAMPZA ER is indicated 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.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve XTAMPZA ER for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.
- XTAMPZA ER is not indicated as an as-needed (prn) analgesic.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

XTAMPZA ER should be prescribed only by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain.

XTAMPZA ER single doses greater than 36 mg (equivalent to 40 mg oxycodone hydrochloride [HCl]) or a total daily dose greater than 72 mg (equivalent to 80 mg oxycodone HCl) are to be administered only to patients in whom tolerance to an opioid of comparable potency has been established. Patients considered opioid tolerant are those receiving, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone HCl per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid.

XTAMPZA ER is administered, twice daily, every 12 hours, and **must be taken with food.** Instruct patients to take XTAMPZA ER capsules with approximately the same amount of food for every dose in order to ensure consistent plasma levels are achieved. *[see Clinical Pharmacology (12.3)]*.

Patients who are unable to swallow XTAMPZA ER should be instructed to sprinkle the capsule contents on soft foods or into a cup and then administer directly into the mouth and immediately swallow. XTAMPZA ER may also be administered through a gastrostomy or nasogastric feeding tube *[see Dosage and Administration 2.6]*.

- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals *[see Warnings and Precautions (5)]*.

- Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse *[see Warnings and Precautions (5.1)]*.

- Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases with XTAMPZA ER and adjust the dosage accordingly *[see Warnings and Precautions (5.2)]*.

The maximum daily dose of XTAMPZA ER is 288 mg per day (eight 36 mg capsules, equivalent to 320 mg oxycodone HCl per day) as the safety of the excipients in XTAMPZA ER for doses over 288 mg/day has not been established.

XTAMPZA ER is formulated with oxycodone base. The following table describes the equivalent amount of oxycodone HCl present in other oxycodone products.

Equivalence table for dosage strengths of oxycodone hydrochloride salt and oxycodone base (XTAMPZA ER)

Oxycodone Hydrochloride	Oxycodone base (XTAMPZA ER)
10 mg	9 mg
15 mg	13.5 mg
20 mg	18 mg
30 mg	27 mg
40 mg	36 mg

2.2 Initial Dosing

Use of XTAMPZA ER as the First Opioid Analgesic (Opioid-Naïve Patients)

Initiate treatment with XTAMPZA ER with one 9 mg capsule orally every 12 hours with food.

Use of XTAMPZA ER in Patients who are not Opioid Tolerant

The starting dose for patients who are not opioid tolerant is XTAMPZA ER 9 mg orally every 12 hours with food.

Use of higher starting doses in patients who are not opioid tolerant may cause fatal respiratory depression *[see Warnings and Precautions (5.2)]*.

Conversion from other Oral Oxycodone Formulations to XTAMPZA ER

Patients receiving other oral oxycodone formulations, may be converted to XTAMPZA ER, using the same total daily dose of oxycodone, by administering one-half of the patient's total daily oral oxycodone dose as XTAMPZA ER every 12 hours with food. Because XTAMPZA ER is not bioequivalent to other oxycodone extended-release products, monitor patients for possible dosage adjustment *[see Dosage and Administration (2.1) and Patient Counseling Information (17)]*.

Conversion from other Opioids to XTAMPZA ER

Discontinue all other around-the-clock opioid drugs when XTAMPZA ER therapy is initiated.

There are no established conversion ratios for conversion from other opioids to XTAMPZA ER defined by clinical trials. Initiate dosing using XTAMPZA ER 9 mg orally every 12 hours with food.

It is safer to underestimate a patient's 24-hour oral oxycodone dosage and provide rescue medication (e.g., immediate-release opioid) than to overestimate the 24-hour oral oxycodone dosage and manage adverse reactions due to an overdose. While useful tables of opioid equivalents are readily available, there is substantial inter-patient variability in the relative potency of different opioid drugs and products.

Conversion from Methadone to XTAMPZA ER

Close monitoring is of particular importance when converting from methadone to other opioid agonists. The ratio between methadone and other opioid agonists may vary widely as a function of previous dose exposure. Methadone has a long half-life and can accumulate in the plasma.

Conversion from Transdermal Fentanyl to XTAMPZA ER

Eighteen hours following the removal of the transdermal fentanyl patch, XTAMPZA ER treatment can be initiated. Although there has been no systematic assessment of such conversion, a conservative oxycodone dose, approximately 9 mg (equivalent to 10 mg oxycodone HCl) every 12 hours of XTAMPZA ER, should be initially substituted for each 25 mcg/hr fentanyl transdermal patch. Follow the patient closely during conversion from transdermal fentanyl to XTAMPZA ER, as there is limited documented experience with this conversion.

2.3 Dosage Modifications in Patients with Hepatic Impairment

For patients with hepatic impairment, start dosing patients at 1/3 to 1/2 the usual starting dose followed by careful dose titration. Monitor closely for adverse events such as respiratory depression. Use of alternate analgesics is recommended for patients who require an XTAMPZA ER dose of less than 9 mg. *[see Use in Specific Populations (8.5), Clinical Pharmacology (12.3)].*

2.4 Titration and Maintenance of Therapy

Individually titrate XTAMPZA ER to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving XTAMPZA ER to assess the maintenance of pain control and the relative incidence of adverse reactions, as well as monitoring for the development of addiction, abuse, and misuse. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration. During chronic therapy, periodically reassess the continued need for the use of opioid analgesics.

Patients who experience breakthrough pain may require a dose increase of XTAMPZA ER or may need rescue medication with an appropriate dose of an immediate-release analgesic. If the level of pain increases after dose stabilization, attempt to identify the source of increased pain before increasing the XTAMPZA ER dose. Because steady-state plasma concentrations are approximated in 1 to 2 days, XTAMPZA ER dosage may be adjusted every 1 to 2 days. If unacceptable opioid-related adverse reactions are observed, the subsequent dose may be reduced. Adjust the dose to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

There are no well-controlled clinical studies evaluating the safety and efficacy with dosing more frequently than every 12 hours. As a guideline, the total daily oxycodone dose usually can be increased by 25% to 50% of the current dose, each time an increase is clinically indicated.

If unacceptable opioid-related adverse reactions are observed, the subsequent dosages may be reduced. Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

2.5 Discontinuation of XTAMPZA ER

When the patient no longer requires therapy with XTAMPZA ER capsules, use a gradual downward titration of the dosage to prevent signs and symptoms of withdrawal in the physically-dependent patient. Do not abruptly discontinue XTAMPZA ER *[see Warnings and Precautions (5.12), Drug Abuse and Dependence (9.2, 9.3)].*

2.6 Administration of XTAMPZA ER

Instruct patients to always take XTAMPZA ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved *[see Dosage and Administration (2.1), Clinical Pharmacology (12.3)].*

For patients who have difficulty swallowing, XTAMPZA ER can also be taken by sprinkling the capsule contents on soft foods or sprinkling the contents into a cup and then administering directly into the mouth or

through a gastrostomy or nasogastric feeding tube. Patients who are unable to swallow a capsule should be instructed to:

1. Open the capsule.
2. Sprinkle the capsule contents (microspheres) onto a small amount of soft food (e.g., applesauce, pudding, yogurt, ice cream, or jam) or into a cup and then administer directly into the mouth and swallow immediately.
3. Rinse the mouth to ensure all capsule contents (microspheres) have been swallowed.
4. Discard the XTAMPZA ER capsule shells after the contents have been sprinkled on soft food or into a cup and then administered directly into the mouth.

The contents of the XTAMPZA ER capsules (microspheres) may be administered through a nasogastric tube or gastrostomy tube. When administering XTAMPZA ER through a nasogastric or gastrostomy tube:

1. Flush the tube with water.
2. Open an XTAMPZA ER capsule and carefully pour the microspheres directly into the tube. Do not pre-mix the capsule contents with the liquid that you will be using to flush them through the tube.
3. Draw up 15 mL of water into a syringe, insert the syringe into the tube, and flush the microspheres through the tube.
4. Repeat the flushing two more times, each with 10 mL of water, to ensure no microspheres remain in the tube.

Alternatively, milk or liquid nutritional supplement may be used as vehicles for flush and administration through feeding tubes.

3 DOSAGE FORMS AND STRENGTHS

XTAMPZA ER capsules contain yellow to light brown microspheres, and each available strength has an outer opaque capsule with colors as identified below.

Strength	**Capsule Description**
9 mg (equivalent to 10 mg oxycodone HCl)	Size 3, ivory cap printed with "XTAMPZA ER" and white body printed with "9 mg"
13.5 mg (equivalent to 15 mg oxycodone HCl)	Size 2, Swedish orange cap printed with "XTAMPZA ER" and white body printed with "13.5 mg"
18 mg (equivalent to 20 mg oxycodone HCl)	Size 1, rich yellow cap printed with "XTAMPZA ER" and white body printed with "18 mg"
27 mg (equivalent to 30 mg oxycodone HCl)	Size 0, light gray cap printed with "XTAMPZA ER" and white body printed with "27 mg"
36 mg (equivalent to 40 mg oxycodone HCl)	Size 00, flesh color cap printed with "XTAMPZA ER" and white body printed with "36 mg"

4 CONTRAINDICATIONS

XTAMPZA ER is contraindicated in patients with:

- Significant respiratory depression *[see Warnings and Precautions (5.2)]*
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment *[see Warnings and Precautions (5.6)]*
- Known or suspected gastrointestinal obstruction, including paralytic ileus *[see Warnings and Precautions (5.10)]*
- Hypersensitivity (e.g., anaphylaxis) to oxycodone.

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse

XTAMPZA ER contains oxycodone, a Schedule II controlled substance. As an opioid, XTAMPZA ER exposes users to the risks of addiction, abuse, and misuse *[see Drug Abuse and Dependence (9)]*. As extended-release products such as XTAMPZA ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present *[see Drug Abuse and Dependence (9)]*.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed XTAMPZA ER. Addiction can occur at recommended dosages and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing XTAMPZA ER, and monitor all patients receiving XTAMPZA ER for the development of these behaviors or conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as XTAMPZA ER, but use in such patients necessitates intensive counseling about the risks and proper use of XTAMPZA ER along with intensive monitoring for signs of addiction, abuse, and misuse.

Abuse or misuse of XTAMPZA ER by snorting or by injecting the dissolved product can result in overdose and death *[see Overdosage (10)]*.

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing XTAMPZA ER. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug *[see Patient Counseling Information (17)]*. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

5.2 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status *[see Overdosage (10)]*. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of XTAMPZA ER, the risk is greatest during the initiation of therapy or following a dosage increase. Closely monitor patients for respiratory depression, especially within the first 24-72 hours of initiating therapy with and following dosage increases of XTAMPZA ER.

To reduce the risk of respiratory depression, proper dosing and titration of XTAMPZA ER are essential *[see Dosage and Administration (2)]*. Overestimating the XTAMPZA ER dose when converting patients from another opioid product can result in a fatal overdose with the first dose.

Accidental ingestion of even one dose of XTAMPZA ER, especially by children, can result in respiratory depression and death due to an overdose of oxycodone.

5.3 Neonatal Opioid Withdrawal Syndrome

Prolonged use of XTAMPZA ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Use in Specific Populations (8.1), Patient Counseling Information (17)]*.

5.4 Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

Concomitant use of XTAMPZA ER with a CYP3A4 inhibitor, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression *[see Warnings and Precautions (5.2)]*, particularly when an inhibitor is added after a stable dose of XTAMPZA ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in XTAMPZA ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using XTAMPZA ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in XTAMPZA ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of XTAMPZA ER until stable drug effects are achieved *[see Drug Interactions (7)]*.

Concomitant use of XTAMPZA ER with CYP3A4 inducers or discontinuation of an CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using XTAMPZA ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur *[see Drug Interactions (7)]*.

5.5 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of XTAMPZA ER with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics *[see Drug Interactions (7)]*.

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than

indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when XTAMPZA ER is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs *[see Drug Interactions (7) and Patient Counseling Information (17)]*.

5.6 Risk of Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

The use of XTAMPZA ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients with Chronic Pulmonary Disease: XTAMPZA ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of XTAMPZA ER [*see Warnings and Precautions (5.2)*].

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients.

Monitor such patients closely, particularly when initiating and titrating XTAMPZA ER and when XTAMPZA ER is given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.2)]*. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of XTAMPZA ER less than 9 mg.

5.7 Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

5.8 Severe Hypotension

XTAMPZA ER may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics) *[see Drug Interactions (7)]*. Monitor these patients for signs of hypotension after initiating or titrating the dosage of XTAMPZA ER. In patients with circulatory shock, XTAMPZA ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of XTAMPZA ER in patients with circulatory shock.

5.9 Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

In patients who may be susceptible to the intracranial effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), XTAMPZA ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with XTAMPZA ER.

Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of XTAMPZA ER in patients with impaired consciousness or coma.

5.10 Risks of Use in Patients with Gastrointestinal Conditions

XTAMPZA ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus.

The oxycodone in XTAMPZA ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

5.11 Risk of Use in Patients with Seizure Disorders

The oxycodone in XTAMPZA ER may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during XTAMPZA ER therapy.

5.12 Withdrawal

Avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including XTAMPZA ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms.

When discontinuing XTAMPZA ER, gradually taper the dosage *[see Dosage and Administration (2.5)]*. Do not abruptly discontinue XTAMPZA ER.

5.13 Risks of Driving and Operating Machinery

XTAMPZA ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of XTAMPZA ER and know how they will react to the medication.

5.14 Laboratory Monitoring

Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative". Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Addiction, Abuse, and Misuse *[see Warnings and Precautions (5.1)]*
- Life-Threatening Respiratory Depression *[see Warnings and Precautions (5.2)]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.3)]*

- Interactions with Benzodiazepines or Other CNS Depressants *[see Warnings and Precautions (5.5)]*
- Adrenal Insufficiency *[see Warnings and Precautions (5.7)]*
- Severe Hypotension *[see Warnings and Precautions (5.8)]*
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.10)]*
- Seizures *[see Warnings and Precautions (5.11)]*
- Withdrawal *[see Warnings and Precautions (5.12)]*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of XTAMPZA ER was evaluated in a Phase 3, randomized-withdrawal, double-blind clinical trial involving 740 patients with moderate-to-severe chronic lower back pain. In the double-blind maintenance phase, 389 patients were randomized and 193 patients were assigned to the XTAMPZA ER treatment group.

The most common AEs (>5%) reported by patients in the Phase 3 clinical trial during the titration phase were: nausea (16.6%), headache (13.9%), constipation (13.0%), somnolence (8.8%), pruritus (7.4%), vomiting (6.4%), and dizziness (5.7%).

The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing XTAMPZA ER with placebo are shown in Table 1 below:

Table 1: Common Adverse Reactions (>5%)

	Titration	Maintenance	
Adverse Reaction	XTAMPZA ER (n = 740) (%)	XTAMPZA ER (n = 193) (%)	Placebo (n = 196) (%)
Nausea	16.6	10.9	4.6
Headache	13.9	6.2	11.7
Constipation	13.0	5.2	0.5
Somnolence	8.8	<1	<1
Pruritus	7.4	2.6	1.5
Vomiting	6.4	4.1	1.5
Dizziness	5.7	1.6	0

In the Phase 3 clinical trial, the following adverse reactions were reported in patients treated with XTAMPZA ER with incidences of 1% to 5%:

Eye disorders: vision blurred

Gastrointestinal disorders: abdominal pain, upper abdominal pain, diarrhea, gastroesophageal reflux disease

General disorders and administration site conditions: chills, drug withdrawal syndrome, fatigue, irritability, edema, pyrexia

Injury, poisoning and procedural complications: excoriation

Metabolism and nutrition disorders: decreased appetite, hyperglycemia

Musculoskeletal and connective tissue disorders: arthralgia, back pain, musculoskeletal pain, myalgia

Nervous system disorders: migraine, tremor

Psychiatric disorders: anxiety, insomnia, withdrawal syndrome

Respiratory, thoracic and mediastinal disorders: cough, oropharyngeal pain

Skin and subcutaneous tissue disorders: hyperhidrosis, rash

Vascular disorders: hot flush, hypertension

In the Phase 3 clinical trial, the following treatment-related adverse reactions were reported in patients treated with XTAMPZA ER with incidences of **less than 1% of patients.**

Investigations: increased gamma-glutamyl transferase, increased heart rate

Nervous system disorders: lethargy, memory impairment, poor-quality sleep

Psychiatric disorders: abnormal dreams, euphoric mood, restlessness

Respiratory, thoracic and mediastinal disorders: dyspnea

Skin and subcutaneous tissue disorders: night sweats

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of oxycodone. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.

Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.

Anaphylaxis: Anaphylaxis has been reported with ingredients contained in XTAMPZA ER.

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids *[see Clinical Pharmacology (12.2)]*.

7 DRUG INTERACTIONS

Table 2 includes clinically significant drug interactions with XTAMPZA ER.

Table 2: Clinically Significant Drug Interactions with XTAMPZA ER

Inhibitors of CYP3A4 and CYP2D6	
Clinical Impact:	The concomitant use of XTAMPZA ER and CYP3A4 inhibitors can increase the plasma concentration of oxycodone, resulting in increased or prolonged opioid effects. These effects could be more pronounced with concomitant use of XTAMPZA ER and CYP2D6 and CYP3A4 inhibitors, particularly when an inhibitor is added after a stable dose of XTAMPZA ER is achieved *[see Warnings and Precautions (5.4)]*. After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the oxycodone plasma concentration will decrease *[see Clinical Pharmacology (12.3)]*, resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to oxycodone.
Intervention:	If concomitant use is necessary, consider dosage reduction of XTAMPZA ER until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals. If a CYP3A4 inhibitor is discontinued, consider increasing the XTAMPZA ER dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal.
Examples:	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g.

	ketoconazole), protease inhibitors (e.g., ritonavir)
CYP3A4 Inducers	
Clinical Impact:	The concomitant use of XTAMPZA ER and CYP3A4 inducers can decrease the plasma concentration of oxycodone *[see Clinical Pharmacology (12.3)]*, resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to oxycodone *[see Warnings and Precautions (5.4)]*. After stopping a CYP3A4 inducer, as the effects of the inducer decline, the oxycodone plasma concentration will increase *[see Clinical Pharmacology (12.3)]*, which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression.
Intervention:	If concomitant use is necessary, consider increasing the XTAMPZA ER dosage until stable drug effects are achieved *[see Dosage and Administration (2.4)]*. Monitor for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider XTAMPZA ER dosage reduction and monitor for signs of respiratory depression.
Examples:	Rifampin, carbamazepine, phenytoin
Benzodiazepines and other Central Nervous System (CNS) Depressants	
Clinical Impact:	Due to additive pharmacological effect, the concomitant use of benzodiazepines or other CNS depressants including alcohol, increases the risk of respiratory depression, profound sedation, coma, and death.
Intervention:	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation *[see Warnings and Precautions (5.5)]*.
Examples	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.
Serotonergic Drugs	
Clinical Impact:	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
Intervention:	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue XTAMPZA ER if serotonin syndrome is suspected.
Examples:	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that effect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Monoamine Oxidase Inhibitors (MAOIs)	

Clinical Impact:	MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma) *[see Warnings and Precautions (5.2)]*.
Intervention:	The use of XTAMPZA ER is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.
Examples:	phenelzine, tranylcypromine, linezolid
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
Clinical Impact:	May reduce the analgesic effect of XTAMPZA ER and/or precipitate withdrawal symptoms.
Intervention:	Avoid concomitant use.
Examples:	Butorphanol, nalbuphine, pentazocine, buprenorphine
Muscle Relaxants	
Clinical Impact:	Oxycodone may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Intervention:	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of XTAMPZA ER and/or the muscle relaxant as necessary.
Diuretics	
Clinical Impact:	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention:	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
Clinical Impact:	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention:	Monitor patients for signs of urinary retention or reduced gastric motility when XTAMPZA ER is used concomitantly with anticholinergic drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome *[see Warnings and Precautions (5.3)]*. There are no available data with XTAMPZA ER in pregnant women to inform a drug-associated risk for major birth defects and miscarriage. In animal reproduction studies, there was no embryo-fetal toxicity when oxycodone hydrochloride was orally administered to rats and rabbits, during the period of organogenesis, at doses 1.3 to 40 times the adult human dose of 60 mg/day, respectively. In a pre- and postnatal toxicity study, when oxycodone was orally administered to rats, there was transiently decreased pup body weight during lactation and the early post-weaning period at the dose equivalent to an adult dose of 160 mg/day. In several published studies, treatment of pregnant rats with oxycodone hydrochloride at clinically relevant doses and below resulted in neurobehavioral effects in offspring *[see Data]*. Based on animal data, advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general

population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/neonatal adverse reactions

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high-pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration of use, and severity of neonatal opioid withdrawal syndrome may vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly *[see Warnings and Precautions (5.3)]*.

Labor or delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid induced respiratory depression in the neonate. XTAMPZA ER is not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, including XTAMPZA ER, can prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression

Data

Animal Data

Studies with oral doses of oxycodone hydrochloride in rats up to 8 mg/kg/day and rabbits up to 125 mg/kg/day, equivalent to 1.3 and 40 times an adult human dose of 160 mg/day, respectively on a mg/m^2 basis, did not reveal evidence of harm to the fetus due to oxycodone. In a pre- and postnatal toxicity study, female rats received oxycodone during gestation and lactation. There were no drug-related effects on reproductive performance in these females or any long-term developmental or reproductive effects in pups born to these rats. Decreased body weight was found during lactation and the early post-weaning phase in pups nursed by dams given the highest dose used (6 mg/kg/day, equivalent to an adult human dose of 160 mg/day, on a mg/m^2 basis). However, body weight of these pups recovered. In published studies, offspring of pregnant rats administered oxycodone hydrochloride during gestation have been reported to exhibit neurobehavioral effects including altered stress responses and increased anxiety-like behavior (2 mg/kg/day IV from Gestation Day 8 to 21 and Postnatal Day 1, 3, and 5; 0.3-times an adult human oral dose of 60 mg/day on a mg/m^2 basis), and altered learning and memory (15 mg/kg/day orally from breeding through parturition; 2.4 times an adult human oral dose of 60 mg/day on a mg/m^2 basis).

8.2 Lactation

Risk Summary

Oxycodone is present in breast milk. Published lactation studies report variable concentrations of oxycodone in breast milk with administration of immediate-release oxycodone to nursing mothers in the early postpartum period. The lactation studies did not assess breastfed infants for potential adverse reactions. Lactation studies have not been conducted with extended–release oxycodone, including XTAMPZA ER, and no information is available on the effects of the drug on the breastfed infant or the effects of the drug on milk production.

Because of the potential for serious adverse reactions, including excess sedation and respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with XTAMPZA ER.

Clinical Considerations

Infants exposed to XTAMPZA ER through breast milk should be monitored for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

8.3 Females and Males of Reproductive Potential

Infertility

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible *[see Adverse Reactions (6.2), Clinical Pharmacology (12.2)]*.

8.4 Pediatric Use

Safety and effectiveness of XTAMPZA ER in pediatric patients below the age of 18 years have not been established.

8.5 Geriatric Use

In controlled pharmacokinetic studies in elderly subjects (greater than 65 years) the clearance of oxycodone was slightly reduced. Compared to young adults, the plasma concentrations of oxycodone were increased approximately 15% *[see Clinical Pharmacology (12.3)]*. Of the total number of subjects entered into the titration phase of the Phase 3 study for XTAMPZA ER (740), 88 (12%) were age 65 and older. In this clinical trial with appropriate initiation of therapy and dose titration, no untoward or unexpected adverse reactions were seen in the elderly patients who received XTAMPZA ER. Thus, the usual doses and dosing intervals may be appropriate for elderly patients. Use caution when selecting a dosage for an elderly patient, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease, and use of other drug therapy.

Respiratory depression is the chief risk in elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of XTAMPZA ER slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression *[see Warnings and Precautions (5.5, 5.6)]*.

8.6 Hepatic Impairment

A study in patients with hepatic impairment demonstrated greater plasma oxycodone concentrations than those seen at equivalent doses in persons with normal hepatic function. A similar effect on plasma oxycodone concentrations can be expected for patients with hepatic impairment taking XTAMPZA ER. Therefore, in the setting of hepatic impairment, start dosing patients at 1/3 to 1/2 the usual starting dose followed by careful dose titration. Use of alternative analgesics is recommended for patients who require a dose of XTAMPZA ER less than 9 mg. *[see Dosage and Administration (2.3), Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

In patients with renal impairment, as evidenced by decreased creatinine clearance (<60 mL/min), the concentrations of oxycodone in the plasma are approximately 50% higher than in subjects with normal renal function. Follow a conservative approach to dose initiation and adjust according to the clinical situation. Use of

alternative analgesics is recommended for patients who require a dose of XTAMPZA ER less than 9 mg. *[see Clinical Pharmacology (12.3)]*.

8.8 Sex Differences

In pharmacokinetic studies with XTAMPZA ER, healthy female subjects demonstrate up to 20% higher oxycodone plasma exposures than males, even after considering differences in body weight or BMI. The clinical relevance of a difference of this magnitude is low for a drug intended for chronic usage at individualized dosages. In the Phase 3 clinical trial there was a greater frequency of typical opioid adverse events for females than males; there was no male/female difference detected for efficacy.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

XTAMPZA ER contains oxycodone, a Schedule II controlled substance.

9.2 Abuse

XTAMPZA ER contains oxycodone, a substance with a high potential for abuse similar to other opioids including fentanyl, hydromorphone, methadone, morphine, and oxymorphone. XTAMPZA ER can be abused and is subject to misuse, addiction, and criminal diversion *[see Warnings and Precautions (5.1)]*.

The high drug content in extended-release formulations adds to the risk of adverse outcomes from abuse and misuse.

All patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

"Drug-seeking" behavior is very common to persons with substance use disorders. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing, or referral, repeated "loss" of prescriptions, tampering with prescriptions, and reluctance to provide prior medical records or contact information for other healthcare provider(s). "Doctor shopping" (visiting multiple prescribers to obtain additional prescriptions) is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Healthcare providers should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

XTAMPZA ER, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful recordkeeping of prescribing information, including quantity, frequency, and renewal requests as required by state and federal law, is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic reevaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Risks Specific to Abuse of XTAMPZA ER

XTAMPZA ER is for oral use only. Abuse of XTAMPZA ER poses a risk of overdose and death. The risk is increased with concurrent use of XTAMPZA ER with alcohol and other central nervous system depressants.

Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

Abuse Deterrence Studies

XTAMPZA ER capsules contain microspheres formulated with inactive ingredients intended to make the formulation more difficult to manipulate for misuse and abuse.

In Vitro Testing

In vitro physical and chemical manipulation studies were performed to evaluate the success of different methods of defeating the extended-release formulation.

Results support that, relative to immediate-release oxycodone tablets, XTAMPZA ER is less susceptible to the effects of grinding, crushing, and extraction using a variety of tools and solvents.

XTAMPZA ER resisted attempts to pass the melted capsule contents or the microspheres suspended in water through a hypodermic needle.

Pharmacokinetic Studies

The pharmacokinetic profile of manipulated XTAMPZA ER capsule contents (36 mg; [equivalent to 40 mg oxycodone HCl]) was characterized following oral (three studies) and intranasal (two studies) administration. The studies were conducted in a randomized, cross-over design. In studies assessing manipulation by crushing, the most effective crushing method identified in previous in vitro studies was applied to the product(s).

Oral Pharmacokinetic Studies, Manipulated and Intact XTAMPZA ER

The effect of two types of product manipulation (crushing and chewing) on XTAMPZA ER pharmacokinetics was measured in three studies.

In one oral pharmacokinetic study, XTAMPZA ER capsule contents were crushed or chewed prior to oral administration in healthy, naltrexone-blocked volunteers. The two comparators in this study were intact XTAMPZA ER capsules and an immediate-release solution of oxycodone at an equivalent dose.

In two oral pharmacokinetic studies, XTAMPZA ER capsule contents were crushed prior to oral administration in healthy, naltrexone-blocked volunteers. The comparators in these studies included intact XTAMPZA ER capsules, intact and crushed reformulated OXYCONTIN (oxycodone hydrochloride) extended-release tablets at an equivalent dose, and crushed immediate-release oxycodone tablets at an equivalent dose.

The data displayed in Table 3 illustrate the findings from the oral pharmacokinetic studies (data were similar for the two oral pharmacokinetic studies comparing XTAMPZA ER to OXYCONTIN). Collectively, the data demonstrated that crushing or chewing XTAMPZA ER prior to administration did not increase the maximum observed plasma concentration (C_{max}) or total exposure ($AUC_{0\text{-}INF}$) relative to dosing the intact product under fed conditions. Relative to immediate-release oxycodone and crushed reformulated OXYCONTIN (oxycodone hydrochloride) extended-release tablets, the C_{max} for all XTAMPZA ER treatments was lower and the T_{max} longer, consistent with an extended-release profile.

Table 3: Oxycodone Pharmacokinetic Parameters, Administration of Manipulated and Intact Dosage Forms (36mg of XTAMPZA ER or equivalent)

	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-INF} (hr•ng/mL)
Treatment	**Oral Pharmacokinetic Study 1**		
Intact XTAMPZA ER Capsules (fed)	62.3 (13.0)	4.0 (1.5-6)	561 (124)
Crushed XTAMPZA ER Capsule Contents (fed)	57.6 (12.6)	4.5 (2.5-6)	553 (134)
Chewed XTAMPZA ER Capsule Contents (fed)	55.6 (10.9)	4.5 (2.5-8)	559 (113)
Immediate-Release Oxycodone Solution (fasted)	115 (27.3)	0.75 (0.5-2)	489 (80.2)
	Oral Pharmacokinetic Study 2		
Intact XTAMPZA ER Capsules (fed)	67.5 (17.6)	3.5 (1.25 – 6.0)	581 (138)
Crushed XTAMPZA ER Capsule Contents (fed)	62.9 (12.6)	4.0 (2.0 – 7.0)	597 (149)
Intact reformulated OXYCONTIN (oxycodone hydrochloride) extended-release tablets (fed)	64.9 (13.8)	5.0 (2.0-10.0)	611 (145)
Crushed reformulated OXYCONTIN (oxycodone hydrochloride) extended-release tablets (fed)	78.4 (12.9)	1.75 (0.5-5.0)	587 (132)
Crushed Immediate-Release Oxycodone Tablets (fed)	79.4 (17.1)	1.75 (0.5-4.0)	561 (146)

Values shown for C_{max} and AUC_{0-INF} are mean (standard deviation); values shown for T_{max} are median (minimum-maximum).

Nasal Pharmacokinetic Studies

The pharmacokinetic profile following intranasal administration of crushed XTAMPZA ER capsule contents was characterized in two clinical studies.

In Nasal Pharmacokinetic Study 1, XTAMPZA ER capsule contents (36 mg) were crushed and intranasally administered by non-dependent, naltrexone-blocked subjects with a history of nasal abuse of opioids. The two comparators in this study were intact XTAMPZA ER capsules (oral) and oxycodone HCl powder (intranasal) at an equivalent dose.

In Nasal Pharmacokinetic Study 2, XTAMPZA ER capsule contents (36 mg) were crushed and intranasally administered by non-dependent subjects with a history of nasal abuse of opioids. The two comparators in this study were intact XTAMPZA ER capsules (oral) and crushed oxycodone immediate-release tablets (intranasal) at an equivalent dose.

The results of Nasal Pharmacokinetic Studies 1 and 2 are comparable and both studies demonstrated that intranasal administration of crushed XTAMPZA ER capsule contents did not result in higher peak plasma concentration (C_{max}) or shorter time to peak concentration (T_{max}) than taking XTAMPZA ER orally. The data from Nasal Pharmacokinetic Study 2 are displayed in Table 4 to represent these findings.

Table 4: Oxycodone Pharmacokinetic Parameters, Nasal Pharmacokinetic Study 2:

Treatment	**C_{max} (ng/mL)**	**T_{max} (hr)**	**AUC_{0-INF} (hr•ng/mL)**
Intact XTAMPZA ER Capsules (oral)	41.0 (10.0)	5.1 (1.6-8.1)	477 (89.6)
Crushed XTAMPZA ER Capsule Contents (nasal)	29.8 (6.6)	5.1 (1.6-12.1)	459 (106)
Crushed Immediate-Release Tablets (nasal)	60.9 (11.9)	2.6 (0.3-6 1)	577 (124)

Values shown for C_{max} and AUC_{0-INF} are mean (standard deviation); values shown for T_{max} are median (minimum-maximum).

Clinical Studies

Oral Abuse Potential Studies:

The oral abuse potential of chewed XTAMPZA ER was evaluated in two studies.

In a randomized, double-blind, active- and placebo-controlled, single-dose, six-way crossover pharmacodynamic study, 52 non-dependent recreational opioid users received orally-administered active and placebo treatment. The six treatment arms were intact XTAMPZA ER (36 mg, fed and fasted); chewed XTAMPZA ER (36 mg, fed and fasted); crushed immediate-release (IR) oxycodone HCl in solution (40 mg, fasted, equivalent to 36 mg of XTAMPZA ER), and placebo. Data for chewed and intact XTAMPZA ER and crushed IR oxycodone in the fasted state are described below.

Drug Liking was measured on a bipolar 100-point Visual Analog Scale (VAS) where 50 represents a neutral response, 0 represents maximum disliking, and 100 represents maximum liking. Response to whether the subject would take the study drug again was also measured on a bipolar 100-point VAS where 50 represents a neutral response, 0 represents the strongest negative response (e.g., 'definitely would not take drug again'), and 100 represents the strongest positive response (e.g., 'definitely would take drug again').

Fifty-two subjects completed the study, and the results are summarized in Table 5. The oral administration of chewed and intact XTAMPZA ER in the fasted state was associated with statistically lower mean Drug Liking and Take Drug Again VAS scores compared with crushed immediate-release oxycodone. In addition, the Drug Liking and Take Drug Again scores were similar for XTAMPZA ER taken in the intact and chewed states.

Table 5: Summary of Maximum Drug Liking and Take Drug Again (E_{max}) Following Oral Administration

		XTAMPZA ER Intact (Fasted)	XTAMPZA ER Chewed (Fasted)	Crushed IR Oxycodone (Fasted)	Placebo
Drug Liking* (E_{max})	Mean (SD)	73.9 (15.10)	73.3 (14.93)	86.40 (12.01)	55.8 (9.94)
	Median (Range)	73.5 (50-100)	73.5 (50-100)	88.5 (52-100)	50.0 (50-86)
Take Drug Again (E_{max})*	Mean (SD)	77.98 (21.07)	77.85 (18.30)	87.69 (12.90)	50.79 (21.41)
	Median (Range)	80.5 (1-100)	81.5 (50-100)	90.5 (50-100)	50.0 (0-100)

* Bipolar scale (0=maximum negative response, 50=neutral response, 100=maximum positive response)
Emax = maximum (peak) effect; ER = extended-release; IR = immediate-release; VAS = visual analogue scale; SD=Standard Deviation.

A prior, similarly-designed study was also conducted to evaluate the oral abuse potential of chewed XTAMPZA ER. Although the oral administration of chewed and intact XTAMPZA ER in the fasted state was associated with statistically lower mean Drug Liking scores compared with crushed immediate-release oxycodone, the results for Take Drug Again showed small differences that were not statistically significant.

Nasal Abuse Potential Study:

In a randomized, double-blind, active- and placebo-controlled, single-dose, four-way crossover pharmacodynamic study, 39 recreational opioid users with a history of intranasal drug abuse received nasally administered active and placebo drug treatment. The four treatment arms were crushed XTAMPZA ER 36 mg

dosed intranasally; intact XTAMPZA ER 36 mg dosed orally; crushed immediate-release oxycodone HCl 40 mg (equivalent to 36 mg of XTAMPZA ER) dosed intranasally; and placebo. Data for intranasal XTAMPZA ER and crushed immediate-release oxycodone are described below.

Thirty-six subjects completed the study. Intranasal administration of crushed XTAMPZA ER was associated with statistically lower mean Drug Liking and Take Drug Again scores compared with crushed immediate-release oxycodone (summarized in Table 6).

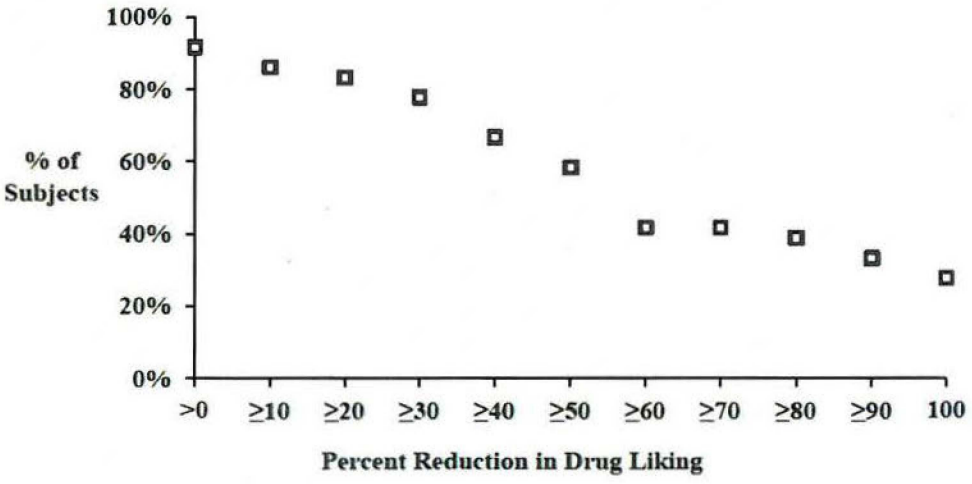
Table 6: Summary of Maximum Drug Liking and Take Drug Again (E_{max}) Following Intranasal Administration

		XTAMPZA ER Intranasal	Crushed IR Oxycodone Intranasal	Placebo
Drug Liking* (E_{max})	Mean (SD)	61.81 (15.64)	82.72 (10.95)	54.5 (11.77)
	Median (Range)	59.5 (16-94)	84 (60-100)	51 (28-93)
Take Drug Again* (E_{max})	Mean (SD)	47.67 (27.84)	71.36 (23.49)	45.92 (17.50)
	Median (Range)	50 (0-100)	78.5 (18-100)	50 (0-97)

* Bipolar scale (0=maximum negative response, 50=neutral response, 100=maximum positive response).
E_{max} = maximum (peak) effect; ER = extended-release; IR = immediate-release; VAS = visual analogue scale; SD=Standard Deviation.

Figure 1 demonstrates a comparison of Drug Liking for intranasal administration of crushed XTAMPZA ER compared to crushed immediate-release oxycodone in subjects who received both treatments (N=36). The Y-axis represents the percent of subjects attaining a percent reduction in drug liking for XTAMPZA ER vs. immediate-release oxycodone greater than or equal to the value on the X-axis. Approximately 92% (n = 33) of subjects had some reduction in drug liking with XTAMPZA ER relative to crushed immediate-release oxycodone HCl. Approximately 78% (n = 28) of subjects had a reduction of at least 30% in drug liking with XTAMPZA ER compared to crushed immediate-release oxycodone HCl, and approximately 58% (n = 21) of subjects had a reduction of at least 50% in drug liking with XTAMPZA ER compared to crushed immediate-release oxycodone HCl.

Figure 1: Percent Reduction Profiles for E_{max} of Drug Liking VAS for Crushed XTAMPZA ER vs. Crushed Immediate-release Oxycodone, N=36 Following Intranasal Administration



Summary

The in vitro data demonstrate that XTAMPZA ER has physicochemical properties expected to make abuse by injection difficult. The data from pharmacokinetic and human abuse potential studies, along with support from the in vitro data, also indicate that XTAMPZA ER has physicochemical properties that are expected to reduce abuse via the oral and intranasal routes. The data from the oral pharmacokinetic studies of crushed or chewed XTAMPZA ER demonstrated a lack of dose dumping with no increase in oxycodone levels compared to intact XTAMPZA ER.

However, abuse of XTAMPZA ER by injection and by the oral and nasal routes of administration is still possible.

Additional data, including epidemiological data, when available, may provide further information on the impact of the current formulation of XTAMPZA ER on the abuse liability of the drug. Accordingly, this section may be updated in the future as appropriate.

XTAMPZA ER contains oxycodone, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit, including fentanyl, hydromorphone, methadone, morphine, and oxymorphone. XTAMPZA ER can be abused and is subject to misuse, addiction, and criminal diversion *[see Warnings and Precautions (5.1) and Drug Abuse and Dependence (9.1)]*.

9.3 Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

XTAMPZA ER should not be abruptly discontinued *[see Dosage and Administration (2.5)]*. If XTAMPZA ER is abruptly discontinued in a physically dependent patient, a withdrawal syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms *[see Use in Specific Populations (8.1)]*.

10 OVERDOSAGE

Clinical Presentation

Acute overdosage with XTAMPZA ER can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen due to severe hypoxia in overdose situations *[see Clinical Pharmacology (12.2)]*.

Treatment of Overdose

In case of overdose, priorities are the reestablishment of a patent and protected airway and institution of assisted or controlled ventilation if needed. Employ other supportive measures (including oxygen, vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life support techniques.

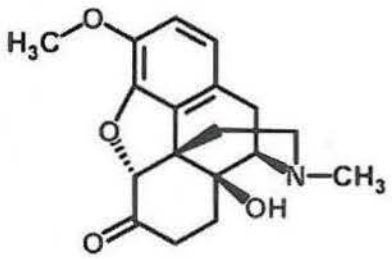
The opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to oxycodone overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdose.

Because the duration of reversal would be expected to be less than the duration of action of oxycodone in XTAMPZA ER, carefully monitor the patient until spontaneous respiration is reliably reestablished. XTAMPZA ER will continue to release oxycodone and add to the oxycodone load for 24 to 48 hours or longer following ingestion necessitating prolonged monitoring. If the response to opioid antagonists is suboptimal or only brief in nature, administer additional antagonist as directed in the product's prescribing information.

In an individual physically dependent on opioids, administration of the usual dosage of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be begun with care and by titration with smaller than usual doses of the antagonist.

11 DESCRIPTION

XTAMPZA ER (oxycodone) extended-release capsules are an opioid agonist for oral use. The capsules contain microspheres formulated with oxycodone base and are supplied in strengths of 9 mg (equivalent to 10 mg oxycodone HCl), 13.5 mg (equivalent to 15 mg oxycodone HCl), 18 mg (equivalent to 20 mg oxycodone HCl), 27 mg (equivalent to 30 mg oxycodone HCl), and 36 mg (equivalent to 40 mg oxycodone HCl) capsules. The capsule strengths describe the amount of oxycodone base per capsule. The structural formula for oxycodone is as follows:



$C_{18}H_{21}NO_4$ MW 315.37 g/mol

The chemical name is 4,5 α-Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one.

Oxycodone base is a white, odorless crystalline powder derived from the opium alkaloid, thebaine. Oxycodone is present as myristate salt in the XTAMPZA ER formulation.

Each XTAMPZA ER capsule contains either 9, 13.5, 18, 27, or 36 mg of oxycodone (equivalent to 10, 15, 20, 30, or 40 mg of oxycodone HCl, respectively) and the following inactive ingredients: myristic acid, yellow

beeswax, carnauba wax, stearoyl polyoxyl-32 glycerides, magnesium stearate, and colloidal silicon dioxide. The capsule shells collectively contain titanium dioxide, hypromellose, and water. Additionally, the 9 mg and 18 mg strength capsule shells contain yellow iron oxide, the 13.5 and 36 mg strength capsule shells contain red iron oxide, and the 27 mg strength capsule shells contain black iron oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Oxycodone is a full opioid agonist and is relatively selective for the mu receptor, although it can bind to other opioid receptors at higher doses. The principal therapeutic action of oxycodone is analgesia. Like all full opioid agonists, there is no ceiling effect to analgesia for oxycodone. Clinically, dosage is titrated to provide adequate analgesia and may be limited by adverse reactions, including respiratory and CNS depression.

The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and are thought to play a role in the analgesic effects of this drug. In addition, when oxycodone binds to mu-opioid receptors, it results in positive subjective effects, such as drug liking, euphoria, and high.

12.2 Pharmacodynamics

Effects on the Central Nervous System

Oxycodone produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to both increases in CO_2 tension and to electrical stimulation.

Oxycodone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations *[see Overdosage (10)]*.

Effects on the Gastrointestinal Tract and Other Smooth Muscle

Oxycodone causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Effects on the Cardiovascular System

Oxycodone produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes and sweating and/or orthostatic hypotension.

Effects on the Endocrine System

Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans *[see Adverse Reactions (6.2)]*. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle,

and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date *[see Adverse Reactions (6.2)]*.

Effects on the Immune System

Opioids have been shown to have a variety of effects on components of the immune system in in vitro and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

Concentration–Efficacy Relationships

Studies in normal volunteers and patients reveal predictable relationships between oxycodone dosage and plasma oxycodone concentrations, as well as between concentration and certain expected opioid effects, such as pupillary constriction, sedation, overall subjective "drug effect," analgesia, and feelings of relaxation.

The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. The minimum effective analgesic concentration of oxycodone for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome, and/or the development of analgesic tolerance *[see Dosage and Administration (2.1, 2.4)]*.

Concentration –Adverse Reaction Relationships

There is a relationship between increasing oxycodone plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions.

12.3 Pharmacokinetics

The activity of XTAMPZA ER is primarily due to the parent drug oxycodone. XTAMPZA ER is designed to provide delivery of oxycodone over 12 hours.

Absorption

XTAMPZA ER is not bioequivalent to oxycodone extended-release tablets. In the fasted state, both peak serum concentration (C_{max}) and extent of absorption (AUC) are lower for XTAMPZA ER, and in the fed state, C_{max} is lower, but AUC is similar.

Compared to immediate-release oxycodone solution dosed under fasted conditions the mean C_{max} of oxycodone from XTAMPZA ER is lower (73% and 43% lower for fasted and fed administration, respectively) and the median time to peak plasma concentration (T_{max}) is approximately 3 hours longer. The extent of absorption of oxycodone from XTAMPZA ER is less than from immediate-release oxycodone oral solution in the fasted state (relative bioavailability of 75%), but comparable in the fed state (relatively bioavailability of 114%).

The peak plasma concentration of oxycodone from XTAMPZA ER occurs approximately 4.5 hours after fed dose administration. Upon repeated dosing with XTAMPZA ER in healthy subjects in pharmacokinetic studies, steady-state levels were achieved within 24-36 hours. Oxycodone is extensively metabolized and eliminated primarily in the urine as both conjugated and unconjugated metabolites. The apparent elimination half-life ($t_{½}$) of oxycodone following the administration of XTAMPZA ER when dosed in the fed state was 5.6 hours compared to 3.2 hours for immediate-release oxycodone.

Food Effects

The oral bioavailability of oxycodone from XTAMPZA ER is greater when taken with food than when taken in the fasted state. The oral bioavailability is dependent on the food consumed and is greatest following a high-fat

and high-calorie meal with an increase in C_{max} of 100-150% and AUC of 50-60% compared to the fasted state. Following a medium-fat medium-calorie meal, the C_{max} increased by 84% and AUC by 28% compared to the fasted state. Following a low-fat low-calorie meal, C_{max} was 19% higher and AUC was comparable, relative to the fasted state.

Pharmacokinetic Profile of XTAMPZA ER Intact and Sprinkled

Plasma concentration over time has been measured following administration of XTAMPZA ER capsule contents intact with food and sprinkled. The pharmacokinetic profile for the capsule contents sprinkled was equivalent to intact capsule administration (Table 7).

Table 7: Oxycodone Pharmacokinetic Parameters, Administration of Capsule Contents and Intact Capsules (36 mg)

Treatment	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-INF} (hr•ng/mL)
Intact XTAMPZA ER Capsules (fed)	55.3 (13.6)	4.5 (1.5 – 9.0)	540 (143)
Sprinkled XTAMPZA ER Capsule Contents (fed)	48.1 (12.0)	4.5 (2.5 – 9.0)	528 (130)

Values shown for C_{max} and AUC_{0-INF} are mean (standard deviation); values shown for T_{max} are median (minimum - maximum).

Distribution

Following intravenous administration, the steady-state volume of distribution (V_{ss}) for oxycodone was 2.6 L/kg. Oxycodone binding to plasma protein at 37°C and a pH of 7.4 was about 45%. Once absorbed, oxycodone is distributed to skeletal muscle, liver, intestinal tract, lungs, spleen, and brain. Oxycodone has been found in breast milk *[see Use in Specific Populations (8.2)]*.

Elimination

In humans, oxycodone is extensively metabolized. Oxycodone and its metabolites are excreted primarily via the kidney.

Metabolism

Oxycodone is extensively metabolized by multiple metabolic pathways to produce noroxycodone, oxymorphone, and noroxymorphone, which are subsequently glucuronidated. Noroxycodone and noroxymorphone are the major circulating metabolites. CYP3A mediated N-demethylation to noroxycodone is the primary metabolic pathway of oxycodone with a lower contribution from CYP2D6-mediated O-demethylation to oxymorphone. Therefore, the formation of these and related metabolites can, in theory, be affected by other drugs *[see Drug Interactions (7)]*.

Noroxycodone exhibits very weak anti-nociceptive potency compared to oxycodone; however, it undergoes further oxidation to produce noroxymorphone, which is active at opioid receptors. Although noroxymorphone is an active metabolite and present at relatively high concentrations in circulation, it does not appear to cross the blood-brain barrier to a significant extent. Oxymorphone is present in the plasma only at low concentrations and undergoes further metabolism to form its glucuronide and noroxymorphone. Oxymorphone has been shown to be active and to possess analgesic activity but its contribution to analgesia following oxycodone administration is thought to be clinically insignificant. Other metabolites (α- and ß-oxycodol, noroxycodol, and oxymorphol) may be present at very low concentrations and demonstrate limited penetration into the brain as compared to oxycodone. The enzymes responsible for keto-reduction and glucuronidation pathways in oxycodone metabolism have not been established.

Excretion

Oxycodone and its metabolites are excreted primarily via the kidney. The amounts measured in the urine have been reported as follows: free and conjugated oxycodone 8.9%, free noroxycodone 23%, free oxymorphone less than 1%, conjugated oxymorphone 10%, free and conjugated noroxymorphone 14%, reduced free and conjugated metabolites up to 18%. The total plasma clearance was approximately 1.4 L/min in adults.

Specific Populations

Age: Geriatric Population

The plasma concentrations of oxycodone are nominally affected by age, being 15% greater in elderly as compared to young subjects (age 21-45).

Sex

Across individual pharmacokinetic studies, oxycodone plasma exposures for female subjects were up to 20% higher than for male subjects, even after considering differences in body weight or BMI. The reason for this difference is unknown *[see Use in Specific Populations (8)]*.

Renal Impairment

Data from a pharmacokinetic study involving 13 patients with mild to severe renal dysfunction (creatinine clearance <60 mL/min) showed peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, and AUC values for oxycodone, noroxycodone, and oxymorphone 60%, 50%, and 40% higher than normal subjects, respectively. This was accompanied by an increase in sedation, but not by differences in respiratory rate, pupillary constriction, or several other measures of drug effect. There was an increase in mean elimination $t_{½}$ for oxycodone of 1 hour.

Hepatic Impairment

Data from a study involving 24 patients with mild to moderate hepatic dysfunction show peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, than healthy subjects. AUC values are 95% and 65% higher, respectively. Oxymorphone peak plasma concentrations and AUC values are lower by 30% and 40%. The mean elimination $t_{½}$ for oxycodone increased by 2.3 hours.

Drug Interaction Studies

CYP3A4 Inhibitors

CYP3A4 is the major enzyme involved in noroxycodone formation. Co-administration of a 10 mg single dose of oxycodone extended –release tablet and the CYP3A4 inhibitor ketoconazole (200 mg BID) increased oxycodone AUC and C_{max} by 170% and 100%, respectively *[see Drug Interactions (7)]*.

CYP3A4 Inducers

A published study showed that the co-administration of rifampin, a drug metabolizing enzyme inducer, decreased oxycodone AUC and C_{max} values by 86% and 63%, respectively *[see Drug Interactions (7)]*.

CYP2D6 Inhibitors

Oxycodone is metabolized in part to oxymorphone via CYP2D6. While this pathway may be blocked by a variety of drugs such as certain cardiovascular drugs (e.g., quinidine) and antidepressants (e.g., fluoxetine), such blockade is not expected to be of clinical significance for XTAMPZA ER *[see Drug Interactions (7)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long term studies in animals to evaluate the carcinogenic potential of oxycodone have not been conducted.

Mutagenesis

Oxycodone was genotoxic in the in vitro mouse lymphoma assay. Oxycodone was negative when tested at appropriate concentrations in the in vitro chromosomal aberration assay, the in vitro bacterial reverse mutation assay (Ames test), and the in vivo bone marrow micronucleus assay in mice.

Impairment of Fertility

In a study of reproductive performance, rats were administered a once daily gavage dose of the vehicle or oxycodone hydrochloride (0.5, 2, and 8 mg/kg). Male rats were dosed for 28 days before cohabitation with females, during the cohabitation and until necropsy (2-3 weeks post-cohabitation). Females were dosed for 14 days before cohabitation with males, during cohabitation and up to Gestation Day 6. Oxycodone HCl did not affect reproductive function in male or female rats at any dose tested ($\leq$ 8 mg/kg/day), up to 1.3 times a human dose of 60 mg/day.

13.2 Animal Toxicology

The safety of beeswax, carnauba wax, and myristic acid in XTAMPZA ER in doses exceeding a total daily dose of 288 mg oxycodone per day (equivalent to 320 mg oxycodone HCl per day) has not been studied.

14 CLINICAL STUDIES

An enriched-enrollment, randomized-withdrawal, double-blind, placebo-controlled, parallel group, study was conducted in 740 patients with persistent, moderate-to-severe chronic lower back pain, with inadequate pain control from their prior therapy. During screening, patients stopped their prior opioid analgesics and/or non-opioid analgesics prior to starting XTAMPZA ER treatment. Patients were titrated to a stable and tolerated dose between 18 mg (equivalent to 20 mg oxycodone HCl) twice daily and 72 mg (equivalent to 80 mg oxycodone HCl) twice daily of XTAMPZA ER in an open-label fashion during the first six weeks of the trial. Optional use of rescue medication (acetaminophen 500 mg tablets) up to 2 tablets every 4-6 hours was permitted during the dose titration phase, up to 2000 mg per day. XTAMPZA ER was titrated once every three to seven days until a stable and tolerable dose was identified (maximum dose of 72 mg [equivalent to 80 mg oxycodone HCl] twice daily).

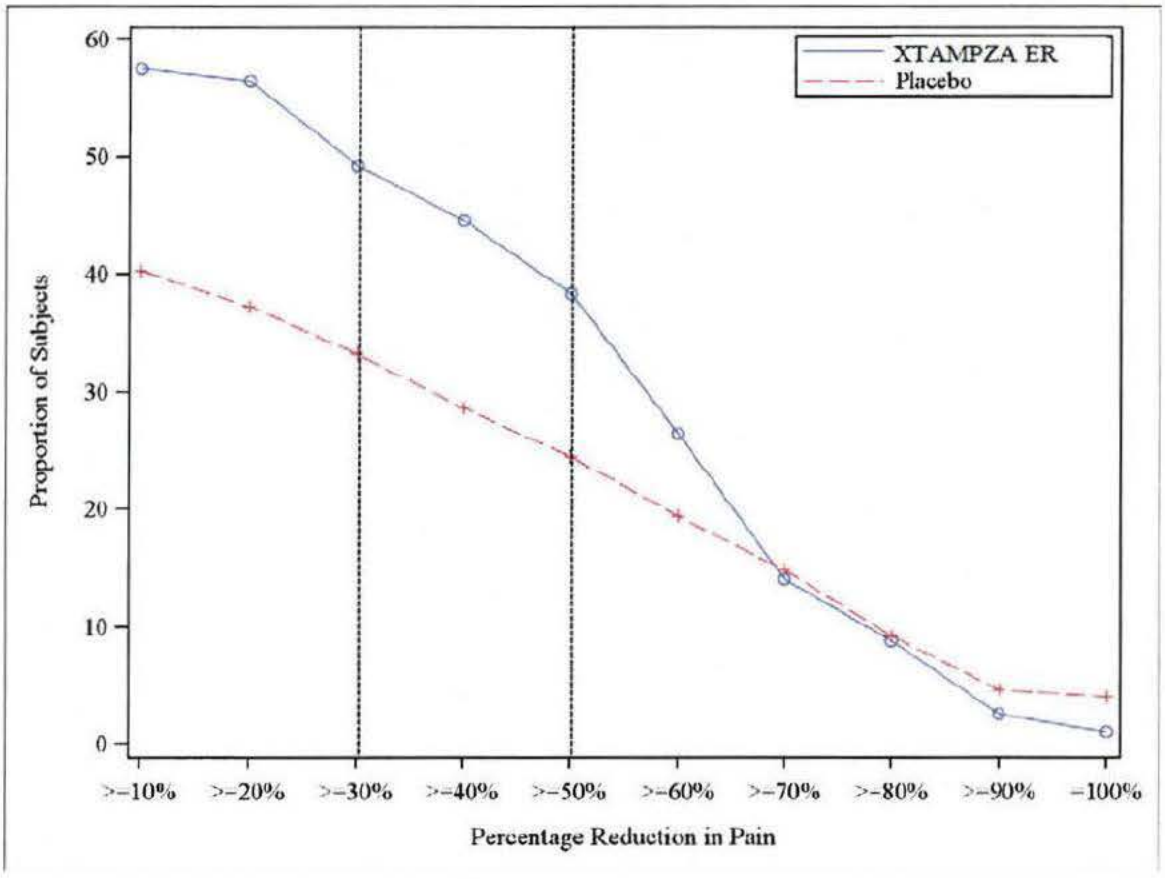
Following the titration phase, 389 subjects (53%) met the study randomization criteria of adequate analgesia (pain reduction of at least 2 points from screening baseline to a score of 4 or less on a 0-10 numerical rating scale) and acceptable tolerability of XTAMPZA ER and entered the randomized, double-blind maintenance phase. Subjects discontinued from the dose-titration phase for the following reasons: failure to meet entrance criteria (18%), adverse events (13%), subject request (7%) and lack of efficacy (5%). Patients were randomized at a ratio of 1:1 into a 12-week double-blind maintenance phase with their fixed stable dose of XTAMPZA ER (or matching placebo). Patients randomized to placebo were given a blinded taper of XTAMPZA ER according to a prespecified tapering schedule; XTAMPZA ER was decreased by 25% to 35% every 5 days for the higher doses of XTAMPZA ER and up to 50% every 5 days for the mid-to-lower doses of XTAMPZA ER over the first 20 days of the double-blind maintenance phase. Patients were allowed to use rescue medication (acetaminophen 500 mg tablets) up to a maximum dose of 2000 mg per day. During the double-blind

maintenance phase, 122 patients (63%) completed the 12-week treatment with XTAMPZA ER and 100 (51%) completed with placebo. Overall, 11% of patients discontinued due to lack of efficacy (4% of XTAMPZA ER patients and 17% of placebo patients), and 7% discontinued due to adverse events (7% of XTAMPZA ER patients and 7% of placebo patients).

In this study, there was a significant difference in pain reduction, favoring XTAMPZA ER, between XTAMPZA ER (doses of 36-144 mg per day, equivalent to 40-160 mg of oxycodone HCl) and placebo, based on the primary endpoint of change in average pain intensity from randomization baseline to Week 12 of the double-blind maintenance phase.

The proportion of patients (responders) in each group who demonstrated improvement in their weekly average pain scores from screening baseline to Week 12, is shown in Figure 2. The figure is cumulative, so that patients whose change from screening is, for example, 30%, are also included at every level of improvement below 30%. Patients who did not complete the study were classified as non-responders. Treatment with XTAMPZA ER resulted in a higher proportion of responders, defined as patients with at least a 30% and 50% improvement as compared to placebo.

Figure 2: Responder Analysis for Pain Intensity: Percent Reduction/Improvement (Intent-to-Treat Population)



16 HOW SUPPLIED/STORAGE AND HANDLING

XTAMPZA ER capsules are supplied in 100-count bottles with a child-resistant closure and as a hospital unit dose package with 10 individually blistered capsules per card; two cards per carton as follows:

Table 8: Summary of XTAMPZA ER Capsule Strengths and Packaging Configurations

Strength	Capsule Description	NDC Number (100-count Bottles with a child-resistant closure)	NDC Number (20-count Hospital Unit Dose Blister Cartons)
9 mg (equivalent to 10 mg oxycodone HCl)	Size 3, ivory cap printed with "XTAMPZA ER" and white body printed with "9 mg"	NDC 24510-110-10	NDC 24510-110-20
13.5 mg (equivalent to 15 mg oxycodone HCl)	Size 2, Swedish orange cap printed with "XTAMPZA ER" and white body printed with "13.5 mg"	NDC 24510-115-10	NDC 24510-115-20
18 mg (equivalent to 20 mg oxycodone HCl)	Size 1, rich yellow cap printed with "XTAMPZA ER" and white body printed with "18 mg"	NDC 24510-120-10	NDC 24510-120-20
27 mg (equivalent to 30 mg oxycodone HCl)	Size 0, light gray cap printed with "XTAMPZA ER" and white body printed with "27 mg"	NDC 24510-130-10	NDC 24510-130-20
36 mg (equivalent to 40 mg oxycodone HCl)	Size 00, flesh color cap printed with "XTAMPZA ER" and white body printed with "36 mg"	NDC 24510-140-10	NDC 24510-140-20

Store at 25°C (77°F); excursions permitted between 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

Dispense in tight, light-resistant container, with child-resistant closure.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling *(Medication Guide).*

Addiction, Abuse, and Misuse

Inform patients that the use of XTAMPZA ER, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death *[see Warnings and Precautions (5.1)]*. Instruct patients not to share XTAMPZA ER with others and to take steps to protect XTAMPZA ER from theft or misuse.

Life-Threatening Respiratory Depression

Inform patients of the risk of life-threatening respiratory depression including information that the risk is greatest when starting XTAMPZA ER or when the dosage is increased, and that it can occur even at recommended dosages *[see Warnings and Precautions (5.2)]*. Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

Accidental Ingestion

Inform patients that accidental ingestion, especially by children, may result in respiratory depression or death *[see Warnings and Precautions (5.2)]*. Instruct patients to take steps to store XTAMPZA ER securely and to dispose of unused XTAMPZA ER by flushing the tablets down the toilet.

Interactions with Benzodiazepines and other CNS Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if XTAMPZA ER is used with benzodiazepines or other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a healthcare provider [*see Warnings and Precautions (5.5), Drug Interactions (7)]*.

Serotonin Syndrome

Inform patients that XTAMPZA ER could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their physicians if they are taking, or plan to take serotonergic medications. *[see Drug Interactions (7)]*.

MAOI Interaction

Inform patients to avoid taking XTAMPZA ER while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking XTAMPZA ER *[see Drug Interactions (7)]*.

Adrenal Insufficiency

Inform patients that XTAMPZA ER could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms *[see Warnings and Precautions (5.7)]*.

Food Effect

Because food has an effect on absorption of oxycodone from XTAMPZA ER, each dose of XTAMPZA ER should be taken with food in order to ensure that appropriate plasma levels are consistently achieved. Instruct patients to take XTAMPZA ER with approximately the same amount of food regardless of whether they swallow the capsule whole or sprinkle on soft food or into a cup and then administer directly into the mouth.

XTAMPZA ER may be taken as intact capsules or, alternately, may be administered as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube *[see Dosage and Administration (2.1,2.6)]*.

Important Administration Instructions *[see Dosage and Administration (2.1, 2.5, 2.6), Warnings and Precautions (5.2)]*

Instruct patients how to properly take XTAMPZA ER, including the following:

- Taking XTAMPZA ER with food
- Swallowing XTAMPZA ER capsules whole or sprinkling the capsule contents on soft food or into a cup and administering directly into the mouth
- Using XTAMPZA ER exactly as prescribed to reduce the risk of life-threatening adverse reactions (e.g., respiratory depression)
- Not discontinuing XTAMPZA ER without first discussing the need for a tapering regimen with the prescriber

Hypotension

Inform patients that XTAMPZA ER may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position) *[see Warnings and Precautions (5.8)]*.

Anaphylaxis

Inform patients that anaphylaxis has been reported with ingredients contained in XTAMPZA ER. Advise patients how to recognize such a reaction and when to seek medical attention *[see Contraindications (4), Adverse Reactions (6)]*.

Pregnancy

Neonatal Opioid Withdrawal Syndrome

Inform female patients of reproductive potential that prolonged use of XTAMPZA ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated *[see Warnings and Precautions (5.3), Use in Specific Populations (8.1)]*.

Embryofetal Toxicity

Advise females of reproductive potential that XTAMPZA ER can cause fetal harm and to inform their healthcare provider of a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.

Lactation

Advise patients that breastfeeding is not recommended during treatment with XTAMPZA ER *[see Use in Specific Populations (8.2)]*.

Infertility

Inform patients that chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible *[see Adverse Reactions (6.2)]*.

Driving or Operating Heavy Machinery

Inform patients that XTAMPZA ER may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication [*see Warnings and Precautions (5.13)]*.

Constipation

Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention.

Disposal of Unused XTAMPZA ER

Advise patients to flush the unused capsules down the toilet when XTAMPZA ER is no longer needed.

Healthcare professionals can telephone Collegium Pharmaceutical's Medical Affairs Department (1-855-331-5615) for information on this product.

Manufactured by: Patheon Pharmaceuticals, Cincinnati, OH 45237

U.S. Patent Nos. 7,399,488; 7,771,707; 8,449,909; 8,557,291; 8,758,813; 8,840,928; 9,044,398, 9,248,195, 9,592,200; 9,682,075; 9,737,530 and 9,763,883.

Medication Guide
XTAMPZA® ER (ex tamp' zah ee ar)
(oxycodone) extended-release capsules, CII

XTAMPZA ER is:

- A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage pain severe enough to require daily, around-the-clock, long-term treatment with an opioid, when other pain treatments such as non-opioid pain medicines or immediate-release opioid medicines do not treat your pain well enough or you cannot tolerate them.
- A long-acting (extended-release) opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed by your healthcare provider, you are at risk for opioid addiction, abuse, and misuse that can lead to death.
- Not for use to treat pain that is not around-the-clock.

Important information about XTAMPZA ER:

- **Get emergency help right away if you take too much XTAMPZA ER (overdose).** When you first start taking XTAMPZA ER, when your dose is changed, or if you take too much (overdose), serious life-threatening breathing problems that can lead to death may occur.
- Taking XTAMPZA ER with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.
- Never give anyone else your XTAMPZA ER. They could die from taking it. Store XTAMPZA ER away from children and in a safe place to prevent stealing or abuse. Selling or giving away XTAMPZA ER is against the law.

Do not take XTAMPZA ER if you have:

- severe asthma, trouble breathing, or other lung problems.
- a bowel blockage or have narrowing of the stomach or intestines.

Before taking XTAMPZA ER, tell your healthcare provider if you have a history of:

- head injury, seizures
- problems urinating
- liver, kidney, thyroid problems
- pancreas or gallbladder problems
- abuse of street or prescription drugs, alcohol addiction, or mental health problems.

Tell your healthcare provider if you are:

- **pregnant or planning to become pregnant.** Prolonged use of XTAMPZA ER during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **breastfeeding.** Not recommended during treatment with XTAMPZA ER. It may harm your baby.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking XTAMPZA ER with certain other medicines can cause serious side effects that could lead to death.

When taking XTAMPZA ER:

- Do not change your dose. Take XTAMPZA ER exactly as prescribed by your healthcare provider. Use the lowest dose possible for the shortest time needed.
- Take your prescribed dose every 12 hours, at the same time every day. Do not take more than your prescribed dose. If you miss a dose, take your next dose at your usual time.
- If you cannot swallow XTAMPZA ER capsules, see the detailed Instructions for Use.
- Always take XTAMPZA ER capsules with approximately the same amount of food to ensure enough medicine is absorbed.
- Swallow XTAMPZA ER whole. Do not snort, or inject XTAMPZA ER because this may cause you to overdose and die.
- The contents of the XTAMPZA ER capsules may be sprinkled on soft food, sprinkled into a cup and then put directly into the mouth, or given through a nasogastric or gastrostomy tube.
- **Call your healthcare provider if the dose you are taking does not control your pain.**
- **Do not stop taking XTAMPZA ER without talking to your healthcare provider.**
- After you stop taking XTAMPZA ER, flush any unused capsules down the toilet.

While taking XTAMPZA ER DO NOT:

- Drive or operate heavy machinery, until you know how XTAMPZA ER affects you. XTAMPZA ER can make you sleepy, dizzy, or lightheaded.
- Drink alcohol or use prescription or over-the-counter medicines that contain alcohol. Using products containing alcohol during treatment with XTAMPZA ER may cause you to overdose and die.

The possible side effects of XTAMPZA ER are:

- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain. Call your healthcare provider if you have any of these symptoms and they are severe.

Get emergency medical help if you have:

- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue, or throat, extreme drowsiness, light-headedness when changing positions, feeling faint, agitation, high body temperature, trouble walking, stiff muscles, or mental changes such as confusion.

These are not all the possible side effects of XTAMPZA ER. Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088. **For more information, go to dailymed.nlm.nih.gov**

Manufactured by: Pa heon Pharmaceuticals, 2110 Galbraith Road, Cincinnati, OH 45237, www.collegiumpharma.com or call 855-331-5615

This Medication Guide has been approved by the U.S. Food and Drug Administration. Issued: December 2016

Instructions for Use

XTAMPZA® ER (ex tamp' zah ee ar)
(oxycodone) extended-release capsules, CII

Always take XTAMPZA ER with approximately the same amount of food. If you cannot swallow XTAMPZA ER capsules, tell your healthcare provider. If your healthcare provider tells you that you can take XTAMPZA ER by sprinkling the capsule contents, follow these steps:

XTAMPZA ER can be opened and the contents inside the capsule can be sprinkled onto soft foods (such as, applesauce, pudding, yogurt, ice cream, or jam) as follows:

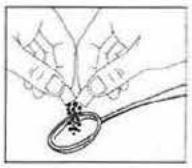


Figure 1

- Open the XTAMPZA ER capsule and sprinkle the contents over about one tablespoon of the soft food listed above (See Figure 1).

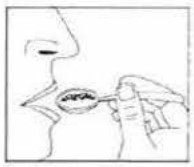


Figure 2

- Swallow all of the soft food and sprinkled capsule contents right away. Do not save any of the soft food and capsule contents for another dose (See Figure 2).

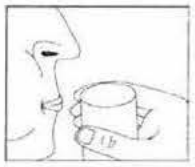


Figure 3

- Rinse your mouth to make sure you have swallowed all of the capsule contents. (See Figure 3).

Figure 4

- Flush the empty capsule down the toilet right away (See Figure 4).

XTAMPZA ER capsule contents can also be sprinkled into a cup and then put directly into the mouth.

Giving XTAMPZA ER through a nasogastric or gastrostomy tube:
Use water, milk, or a liquid nutritional supplement to flush the tube when giving XTAMPZA ER.

Step 1: Flush the nasogastric or gastrostomy tube with liquid.

Step 2: Open an XTAMPZA ER capsule and carefully pour the contents of the capsule directly into the tube. **Do not** pre-mix the capsule contents with the liquid used to flush the capsule contents through the tube.

Step 3: Draw up 15 mL of liquid into a syringe, insert the syringe into the tube, and flush the contents of the capsule through the tube to give the dose.

Step 4: Flush the tube two more times, each time with 10 mL of liquid, to ensure that none of the contents of the capsule are left in the tube.

This Instruction for Use has been approved by the U.S. Food and Drug Administration. Issued: December 2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 208090/S-004

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sharon Hertz, MD
Subject	Division Director Summary Review
NDA #	208090
Applicant Name	Collegium Pharmaceuticals, Inc.
Date of Submission	October 4, 2016
PDUFA Goal Date	November 4, 2017
Proprietary Name / Established (USAN) Name	Xtampza ER/ Oxycodone Extended-Release Capsules
Dosage Forms / Strength	Capsules, 9 mg, 13.5 mg, 18 mg, 27 mg, and 36 mg of oxycodone base, equivalent 10, 15, 20, 30, and 40 mg oxycodone hydrochloride
Proposed Indication(s)	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.
Action:	Approval

Material Reviewed/Consulted: OND Action Package, including:	
OCP	Srikanth C. Nallani, PhD, Yun Xu, PhD
Controlled Substance Staff	James M Tolliver, PhD, Silva Calderon, PhD, Dominic Chiapperino, PhD
OB/DBVI	Anna Sun, PhD, Qianyu Dang, PhD, Yi Tsong, PhD
OPDP/DCDP	Koung Lee, RPh, MS, Sam Skariah, PharmD

OND=Office of New Drugs
DMEPA=Division of Medication Errors Prevention
CDTL=Cross-Discipline Team Leader
DCDP=Division of Consumer Drug Promotion
DMPP=Division of Medical Policy Programs
ORP =Office of Regulatory Policy
OSE= Office of Surveillance and Epidemiology
DSI=Division of Scientific Investigations
OPDP=Office of Prescription Drug Promotion
OMP=Office of Medical Policy Initiatives
DPMH =Division of Pediatric and Maternal Health

Reference ID: 4177789

Signatory Authority Review

1. Introduction

Collegium Pharmaceutical, Inc. has submitted a supplemental 505(b)(2) new drug application for Xtampza ER (oxycodone extended-release capsules), an extended-release formulation of oxycodone with properties intended to deter abuse by the oral, intranasal and intravenous routes of administration. The supplement consists of two new studies, an oral pharmacokinetic study (CP-OXYDET-29) and an oral human abuse liability study (CP-OXYDET-28), both comparing Xtampza and reformulated OxyContin after chewing. A study comparing the pharmacokinetics of Xtampza and OxyContin had been previously submitted and reviewed, (CP-OXYDET-25), however, the approved labeling only includes data comparing manipulated Xtampza and immediate-release oxycodone. The second pharmacokinetic study along with the new oral abuse liability study are intended to add comparative data relative to OxyContin into the label.

2. Background

Xtampza ER was approved on April 26, 2016 based on adequate evidence of efficacy and safety to support approval for the proposed indication, along with evidence to support that Xtampza ER has properties likely to deter abuse by the intranasal and intravenous routes of administration. What was particularly notable from the data submitted in the original NDA is that this formulation was shown to be resistant to dose dumping when chewed or crushed, and it was safe to sprinkle the contents of the capsule on soft food for dosing in patients with dysphagia. The lack of dose dumping in the setting of chewing or crushing is a finding that is a potential safety advantage that benefits the intended patient population for Xtampza ER over other, currently approved extended-release oxycodone products. These properties are the result of the novel formulation, containing a large amount of waxes and myristic acid. Limited nonclinical data for these excipients, however, resulted in the recommendation to limit the maximum daily dose of Xtampza ER to the equivalent of 320 mg of oxycodone hydrochloride per day. This amount is likely to be more than the total daily dose needed by the majority of patients who use opioid analgesics on a chronic basis. There are ongoing post-marketing studies to provide additional safety qualification for the novel excipients.

Xtampza ER has a food effect that is greater than the listed drug referenced by the Applicant in the original application. This was a topic for discussion at a joint meeting of the Anesthesia and Analgesia Drug Product Advisory Committee and the Drug Safety and Risk Management Advisory Committee held on September 11, 2015, and the committee voted 23-0 in favor of approving this product. The committee members were reassured by the safety data from the adequate and well-controlled efficacy study conducted by the Applicant, noting that, while patients did not take Xtampza ER consistently with regard to food as directed, there were no signs that this lack of consistency created any safety problems.

As with all products currently labeled with abuse-deterrent features, the active opioid drug substance can be extracted from Xtampza ER using a variety of methods and volumes of solvent that are incompatible with the usual practice of intravenous administration of a drug of abuse. Some consider these large volume extractions risky for oral abuse. However, the standard for labeling an extended-release opioid product as having properties expected to deter abuse by the oral route has been based on a human abuse potential studies of chewed or crushed product compared to an immediate-release formulation of the same opioid.[1] Taking prescription opioids intact and chewed or crushed has been associated with the oral abuse of extended-release opioid analgesics.[2]

3. CMC/Device

No new CMC data were submitted with this submission.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical data were submitted with this resubmission.

5. Clinical Pharmacology

See Section 11 Abuse Deterrence for review of the clinical pharmacology data.

6. Clinical Microbiology

N/A

7. Clinical/Statistical-Efficacy

No new clinical data were submitted in support of this application. See the discussion of the efficacy data supporting this application in the first summary memo appended below.

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[1] See Hysingla ER (hydrocodone bitartrate) extended-release tablets, approved Nov. 10, 2014, Section 9.2 of package insert, "The data from the clinical abuse potential studies, along with support from the *in vitro* data, also indicate that HYSINGLA ER has physicochemical properties that are expected to reduce intranasal abuse and oral abuse when chewed. However, abuse of HYSINGLA ER by the intravenous, intranasal, and oral routes is still possible." https://www.accessdata fda.gov/drugsatfda_docs/label/2016/206627s004lbl.pdf

[2] Omidian A, Mastropietro DJ, Omidian H (2014) Reported Methods of Abuse for Common Prescription Analgesic Opioids. J Develop Drugs 3:120. doi:10.4172/2329-6631.1000120

8. Safety

No new clinical data were submitted in support of this application. See the discussion of the safety data supporting this application in the first summary memo appended below.

9. Advisory Committee

A second advisory committee was not convened for this submission.

10. Pediatrics

The previously agreed upon waiver of pediatric studies for ages birth to less than 2 years and release from the requirements to conduct studies in ages 2-7 years and 7-17 years have not been changed.

11. Other Relevant Regulatory Issues

REMS

Xtampza ER is part of the Extended-release and Long-acting Opioid Analgesic REMS and will be subject to the existing postmarketing required studies to evaluate the risks of abuse, misuse, overdose and death, as well as for follow-up of the effects of the abuse-deterrent properties.

Patent Certification

The Applicant has provided Paragraph IV certifications as to each patent listed in the Orange Book for OxyContin.

Purdue Pharma L.P.'s initiated an infringement action against Collegium Pharmaceutical, Inc., within 45 days of receiving notice of the paragraph IV certifications to U.S. Patent Nos. 9,522,919 (the '919 patent) and 9,073,933 (the '933 patent) on or about August 28, 2017. The Agency has made the determination that a 30-month stay of approval of NDA 208090 /Supplement 004 is not available because information on the '919 and '933 patents was submitted to FDA after the date of submission of the original NDA 208090 for Xtampza ER (see section 505(c)(3)(C) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)).

Abuse Deterrence

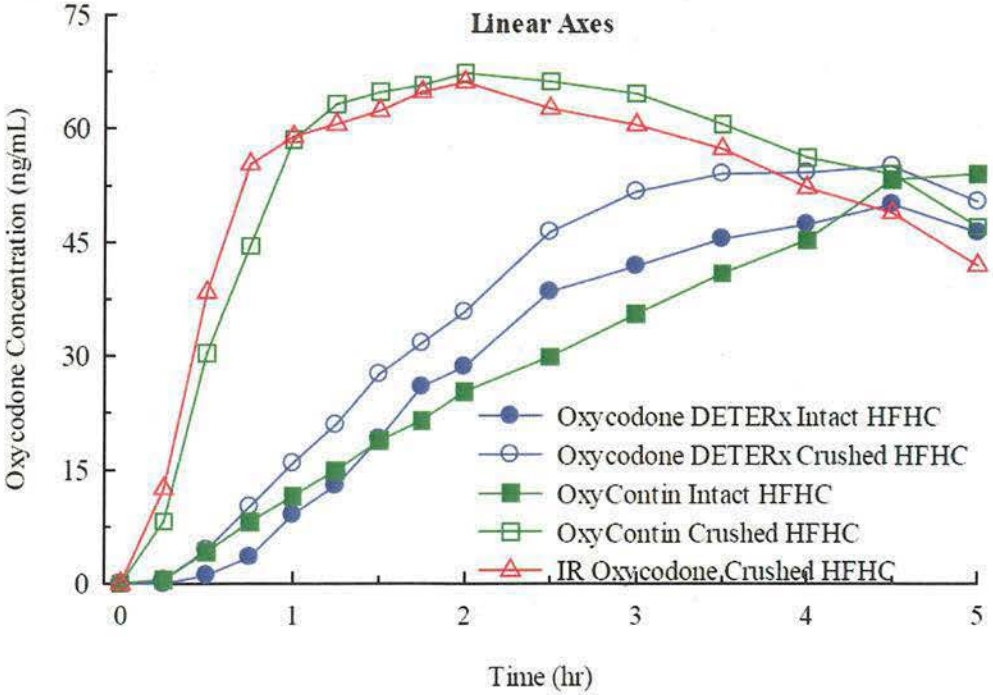
Previously, the applicant had conducted a Category 2 pharmacokinetic study, CP-OXYDET-25 (Study 25) which compared the effect of crushing on the PK for Xtampza and OxyContin (Oxycodone extended-release tablets) when administered after a meal. The results of this study were not included in labeling because replicated data are required for a comparative

claim. Study CP-OXYDET-29 (Study 29), a Category 2 pharmacokinetic study comparing Xtampza and OxyContin fed following chewing in healthy, naltrexone-blocked subjects using a tampering method known to result in particle size reduction in vitro, was conducted to confirm the results from Study 25.

The results of Study 29 are reproduced from Dr. Nallani's review:

> In this study, intact Xtampza was bioequivalent to intact OxyContin fed (Oxycodone extended-release tablets) in fed state. Highest plasma levels were noted with crushed immediate release oxycodone tablets (mean Cmax = 78 ng/mL) and crushed OxyContin fed (Oxycodone extended-release tablets) tablets (mean Cmax = 80 ng/mL) administered orally. It should be noted that OxyContin fed (Oxycodone extended-release tablets) does not have oral abuse deterrence claims in the product label. The median Tmax for intact Xtampza was 3.5 hours and for OxyContin fed (Oxycodone extended-release tablets) it was 4.5 hours. It is noteworthy to mention an observed Tlag with all treatments, taken with food, as shown in the table below. Crushing of Oxycodone DETERx or Xtampza resulted in mean C_{max} and AUC values that were bioequivalent and a median Tmax that was unchanged (3.5 hours) relative to intact dosing. The mean concentration versus time profile for oxycodone is displayed on a linear scale below following different treatments over the first five hours for emphasis.

Figure: Mean Oxycodone Profile over the First Five Hours from Study CP-OXYDET-29.



HFHC=high-fat, high-calorie; IR=immediate-release; PK=pharmacokinetic
Source: Appendix 16.6.1, Figure 2

Reference ID: 4177789

Table: Descriptive Statistics of Oxycodone PK Parameters from Study CP-OXYDET-29.

Parameter*	Oxycodone DETERx Intact HFHC	Oxycodone DETERx Crushed HFHC	OxyContin Intact HFHC	OxyContin Crushed HFHC	IR Oxycodone Crushed HFHC
Tlag (h)	0.88 (38)	0.50 (39)	0.50 (38)	0.25 (39)	0.25 (37)
	[0.50 – 1.75]	[0.25 – 1.00]	[0.25 – 1.00]	[0.25 – 0.50]	[0.25 – 0.50]
Cmax (ng/mL)	56.9 ± 13.4 (38)	61.2 ± 13.1 (39)	63.7 ± 14.8 (38)	79.9 ± 17.9 (39)	78.1 ± 22.0 (37)
Tmax (h)	3.50 (38)	3.50 (39)	4.51 (38)	1.75 (39)	1.50 (37)
	[1.00 – 05.5]	[2.50 – 5.50]	[1.75 – 8.00]	[0.50 – 4.50]	[0.50 – 4.53]
AUC(0-t) (hr×ng/mL)	517 + 145 (38)	539 + 144 (39)	566 + 150 (38)	531 + 141 (39)	487 + 137 (37)
AUC(inf) (hr×ng/mL)	534 + 142 (37)	549 + 143 (39)	574 + 150 (38)	540 + 142 (39)	497 + 143 (37)
λz (1/h)	0.1260 ± 0.0221 (37)	0.1404 ± 0.0184 (39)	0.1705 ± 0.0254 (38)	0.1733 ± 0.0307 (39)	0.1887 ± 0.0335 (37)
$t_{1/2}$ (h)	5.68 ± 1.12 (37)	5.02 ± 0.63 (39)	4.15 ± 0.59 (38)	4.13 ± 0.76 (39)	3.78 ± 0.66 (37)
CL/F (L/h)	72.7 ± 23.6 (37)	70.0 ± 19.6 (39)	66.9 ± 18.9 (38)	71.6 ± 21.5 (39)	82.8 ± 44.9 (37)
Vz/F (L)	597 ± 235 (37)	503 ± 145 (39)	393 ± 94.3 (38)	416 ± 110 (39)	430 ± 174 (37)
Fr (%)	120 + 93.2 (35)	126 + 100 (36)	130 + 104 (36)	124 + 100 (37)	†

*Arithmetic mean ± standard deviation (N) except T_{lag} and T_{max} for which the median (N) [Range] is reported.
†Not applicable as IR Oxycodone Crushed HFHC was the reference treatment.

CV = coefficient of variation; Extrap = Extrapolated; HFHC = high-fat, high-calorie; IR = immediate-release; Max = maximum; Min = minimum; n = number of subject used in the calculation; NA = not applicable; PK = pharmacokinetic; SD = standard deviation

Source: Appendix 16.6.1, Table 2

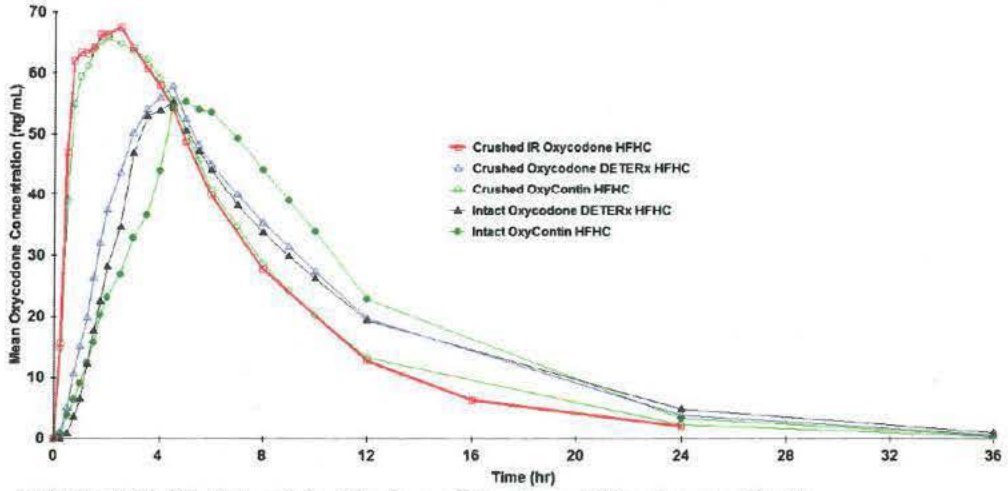
The excerpt from Dr. Nallani's review continues:

> Statistical analysis showing bioequivalence comparison of oxycodone Cmax, AUC parameters is presented in the table below. The sponsor conducted primary comparisons with oral IR oxycodone 40 mg as reference; however, secondary analysis comparisons with intact Xtampza taken with food were also used in the review. In this study, conducted under fed-state, the peak plasma levels of oral OxyContin fed (Oxycodone extended-release tablets) administered after crushing resulted in 25% higher plasma levels at median Tmax of 1.75 hours compared to intact OxyContin fed (Oxycodone extended-release tablets) taken orally with a Tmax of 4.5 hours. According to the bioequivalence analysis using IR oxycodone crushed taken with food as reference,
> a) Crushed Xtampza has 20% lower Cmax compared to IR, overall AUC is comparable across treatments.
> b) Crushed OxyContin fed (Oxycodone extended-release tablets) has similar Cmax and AUC as demonstrated by the 90% CI for geometric mean ratio being within 80 -125%.
> c) using crushed OxyContin fed (Oxycodone extended-release tablets) as reference, crushed Xtampza has 24% lower Cmax and similar AUC. However, Tmax of crushed OxyContin fed (Oxycodone extended-release tablets) was noted at a median of 1.75 hours compared to 3.5 hours for crushed Xtampza (See table above on page 5).

See Dr. Nallani's review, page 6 for the table of the bioequivalence analysis. The findings of Study 29 are consistent with the results of Study 25, reproduced from page 24 of my Summary Memo dated October 12, 2015, appended to my Summary Memo dated April 26, 2016.

Reference ID: 4177789

Figure 8: Oxycodone PK Profile following intact and crushed administration of Xtampza and OxyContin, compared to Crushed IR oxycodone after high-fat meal, Study CP-OXYDET-25.



HFHC = high-fat, high-calorie, IR = immediate-release; PK = pharmacokinetic.
Source: Study CP-OXYDET-25 Pharmacokinetic Report. Figure 1 or Figure 2 (with error bars).

In the original application, the applicant submitted Study CP-OXYDET-24 (Study 24), an oral human abuse potential study that compared Xtampza intact and chewed, fasted and fed, with fasted immediate-release (IR) oxycodone and placebo in non-dependent, recreational opioid users. The results of Study 24 are presented in the following table and figures taken from pages 25 through 27 of my Summary Memo dated October 12, 2015. The pharmacokinetic data show that there were a lower C_{max} and longer T_{max} for all conditions of oral Xtampza compared to IR oxycodone.

Table 8. Descriptive Statistics of Plasma Oxycodone Pharmacokinetic Parameters, CP-OXYDET-24.

Oxycodone PK Parameter	Statistic	Xtampza ER 40 mg Intact Fed	Xtampza ER 40 mg Intact Fasted	Xtampza ER 40 mg Chewed Fed	Xtampza ER 40 mg Chewed Fasted	IR Oxycodone 40 mg Crushed Solution Fasted
C_{max} (ng/mL)	Mean (SD)	41.9 (12.4)	30.9 (9.91)	40.3 (12.2)	35.5 (12.5)	77.7 (24.5)
T_{max} (h)	Median (Range)	5.12 (1.6 – 12.1)	4.08 (1.57 – 8.08)	5.07 (2.05 – 12.10)	3.07 (1.07 – 6.17)	1.08 (0.17 – 5.10)
$AUC_{0\text{-}5hrs}$ (h·ng/mL)	Mean (SD)	5.29 (7.37)	17.48 (8.80)	19.54 (13.88)	33.98 (17.56)	111.58 (36.79)
$AUC_{0\text{-}inf}$ (h·ng/mL)	Mean (SD)	553 (131)	469 (107)	515 (122)	467 (126)	467 (106)

(Source: Table 56 on page 169 of the Clinical Study Report for Protocol CP-OXYDET-24)

The results for Drug Liking and Drug High were substantially lower for all conditions of Xtampza compared to IR oxycodone.

Reference ID: 4177789

Figure 11. Mean Drug Liking Scores (Bipolar Scale) over time PD Population, N=38, CP-OXYDET-24

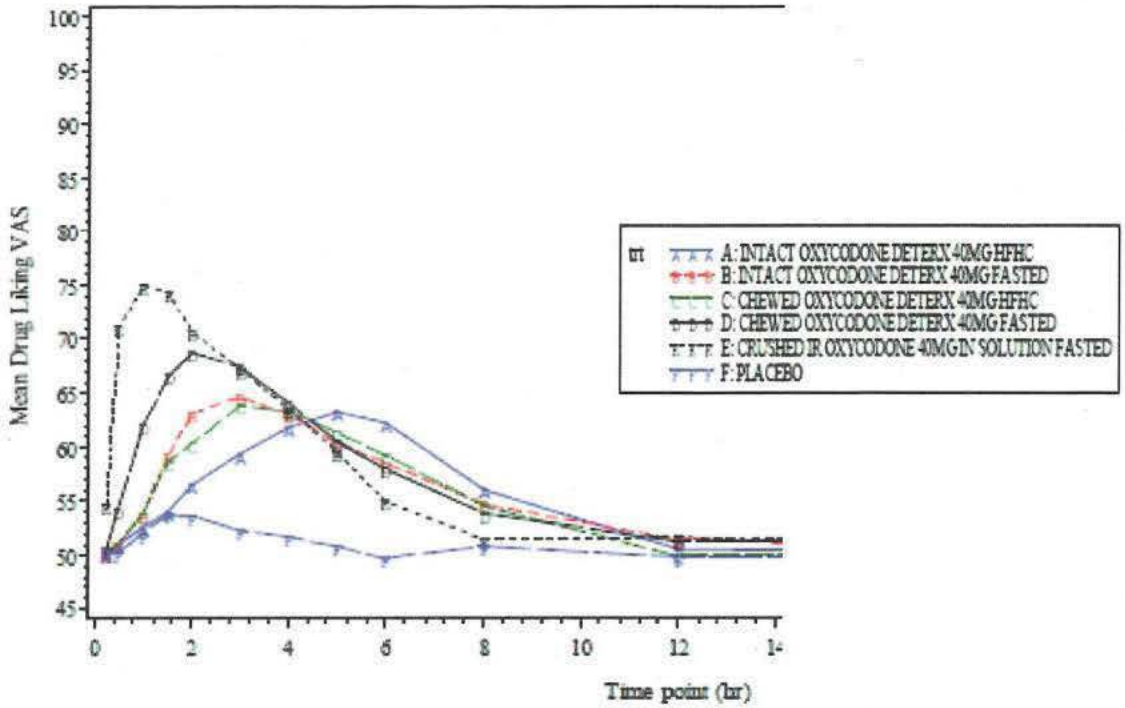
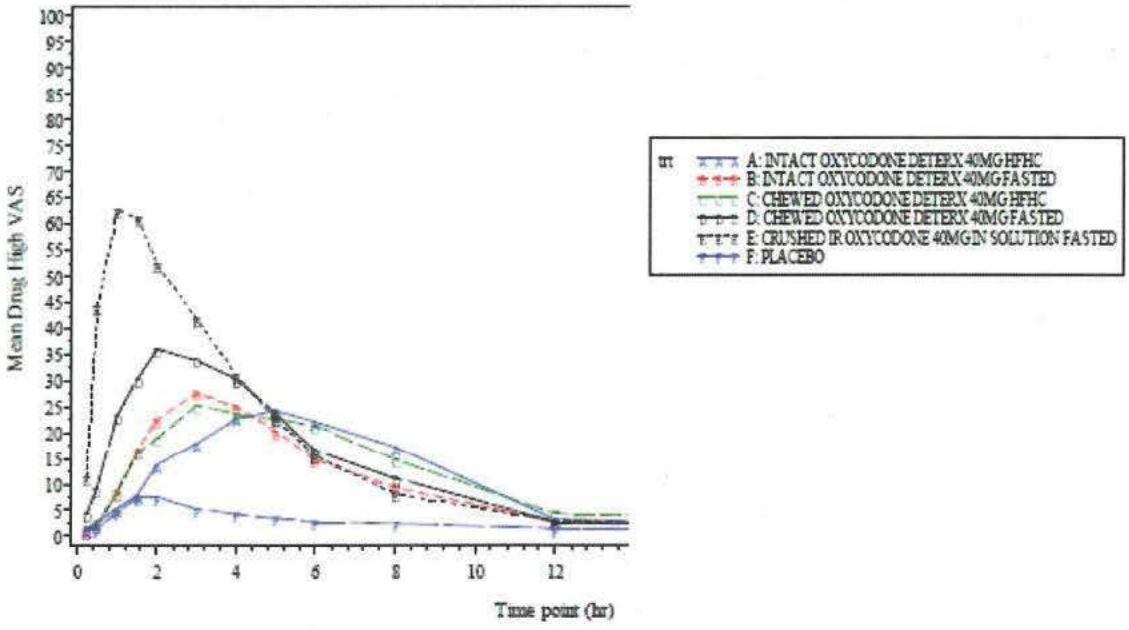


Figure 12. Mean Scores over time for Drug High (Unipolar Scale), PD Population, N=38, CP-OXYDET-24



Reference ID: 4177789

Even with the clear separation in Drug Liking and Drug High scores for Xtampza compared to IR oxycodone, and the differences in the pharmacokinetic profile, the scores for Take Drug Again showed little difference between the chewed Xtampza in the fasted or fed state and immediate-release oxycodone.

Table 9. Descriptive Statistics for E_{max} of Take Drug Again (Bipolar Scale), PD Population (N=38), CP-OXYDET-24.

Treatment	0-100 Point Bipolar Take Drug Again VAS (mm)						
	Mean E_{max}	Standard Deviation	Minimum	First Quartile	Median	Third Quartile	Maximum
A: Intact Xtampza ER 40mg Fed	70.58	18.12	26.00	50.00	74.00	85.00	99.00
B: Intact Xtampza ER 40mg Fasted	70.18	15.96	50.00	52.00	68.50	83.00	98.00
C: Chewed Xtampza ER 40mg Fed	69.26	18.90	3.00	57.00	69.00	84.00	98.00
D: Chewed Xtampza ER 40mg Fasted	73.74	14.92	50.00	63.00	74.00	87.00	98.00
E: Crushed IR Oxycodone HCl 40mg Solution Fasted	75.45	16.79	37.00	64.00	75.50	90.00	100.00
F: Placebo	52.66	13.35	3.00	50.00	50.00	50.00	95.00

As a result of the pharmacodynamic data, no oral abuse-deterrent labeling was permitted for Xtampza. However, the lack of dose dumping with chewing was considered an important safety feature that could benefit patients and the pharmacokinetic data were included in the labeling.

Study CP-OXYDET-28 (Study 28) is a second Category 3 oral abuse potential study. Study 28 compared intact and chewed Xtampza, fed and fasted, IR oxycodone solution (fasted), and placebo. There were similarities between Study 24 and Study 28, but Study 28 utilized more of the recommendations from the final FDA guidance for industry, Abuse-Deterrent Opioids, Evaluation and Labeling.[3] In particular, for Study 28, the applicant changed the dose of oxycodone from 20 mg to 40 mg in the Drug Discrimination Phase and improved training on the pharmacodynamic assessments. In addition, the Drug Discrimination criteria were refined, including a higher minimum Drug Liking Emax response to oxycodone and narrower placebo response range, to ensure that an appropriately sensitive population was selected for enrollment into the Double-blind Treatment Phase.

The pharmacokinetic data from Study 28 demonstrated a higher mean C_{max} was for crushed IR oxycodone compared to all Xtampza treatments. T_{max} was earlier for IR oxycodone than for Xtampza. The food effect previously observed for Xtampza was again demonstrated in Study 28. The following table and figure from Dr. Nallani's review provide the pharmacokinetic data from this study.

[3] https://www.fda.gov/downloads/Drugs/Guidances/UCM334743.pdf

Reference ID: 4177789

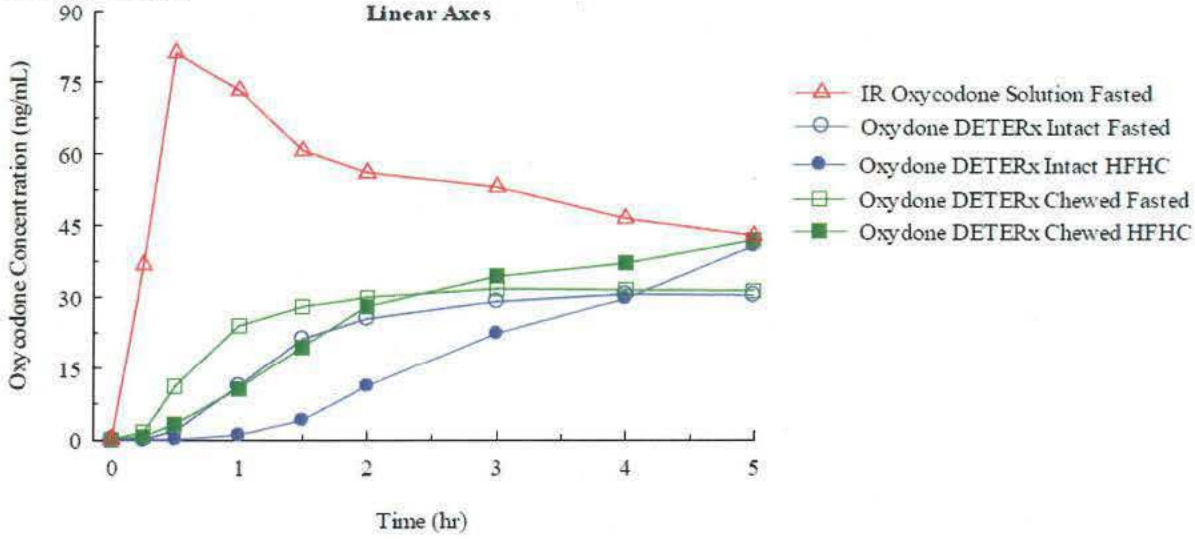
Table: Descriptive Statistics of Oxycodone PK Parameters in Study CP-OXYDET-28.

Parameter*	Oxycodone DETERx Intact HFHC	Oxycodone DETERx Intact Fasted	Oxycodone DETERx Chewed HFHC	Oxycodone DETERx Chewed Fasted	IR Oxycodone Solution Fasted
Tlag (hr)	1.55 (61)	0.55 (67)	0.53 (66)	0.30 (67)	0.30 (64)
	[0.55 – 4.07]	[0.30 – 3.07]	[0.30 – 1.08]	[0.30 – 0.57]	[0.30 – 0.38]
Cmax (ng/mL)	45.4 ± 11.6 (61)	33.9 ± 9.79 (67)	44.3 ± 10.9 (66)	37.6 ± 11.5 (67)	91.1 ± 26.6 (64)
Tmax (hr)	5.07 (61)	4.05 (67)	5.07 (66)	3.07 (67)	0.54 (64)
	[2.07 – 12.1]	[1.52 – 8.07]	[1.52 – 8.07]	[0.53 – 8.07]	[0.30 – 5.15]
AUC(0-t) (hr×ng/mL)	541 ± 127 (61)	447 ± 119 (67)	553 ± 149 (66)	466 ± 145 (67)	543 ± 131 (64)
AUC(inf) (hr×ng/mL)	546 ± 134 (52)	478 ± 122 (63)	568 ± 138 (54)	480 ± 126 (63)	549 ± 132 (63)
λz (1/hr)	0.1332 ± 0.0184 (52)	0.0918 ± 0.0231 (63)	0.1303 ± 0.0171 (54)	0.0993 ± 0.0256 (63)	0.1679 ± 0.0226 (63)
$t^{1}/_{2}$ (hr)	5.30 ± 0.74 (52)	8.14 ± 2.47 (63)	5.42 ± 0.79 (54)	7.57 ± 2.50 (63)	4.21 ± 0.58 (63)
CL/F (L/hr)	69.7 ± 17.3 (52)	80.0 ± 21.0 (63)	67.1 ± 17.0 (54)	79.9 ± 21.1 (63)	69.2 ± 17.0 (63)
Vz/F (L)	528 ± 131 (52)	944 ± 388 (63)	516 ± 112 (54)	874 ± 379 (63)	411 ± 80.3 (63)
Fr (%)	102 ± 15.2 (48)	88.2 ± 21.3 (55)	106 ± 14.2 (49)	89.6 ± 18.3 (59)	†

*Arithmetic mean ± standard deviation (N) except Tlag and Tmax for which the median (N) [Range] is reported.
†Not applicable as IR Oxycodone Solution Fasted was the reference treatment.
HFHC = high-fat, high-calorie meal. IR = immediate-release; PK = pharmacokinetic.

Source: Listing 9.

Figure: Mean Oxycodone PK Profile, Over First Five Hours for Emphasis, in Study CP-OXYDET-28)



The pharmacodynamic endpoints from Study 28 showed lower scores for Xtampza for the Drug Liking VAS, High VAS, Take Drug Again VAS, and Overall Drug Liking VAS as compared to IR oxycodone. The following table is modified from the review by Dr. Sun.

Reference ID: 4177789

Table 1. E_{max} Descriptive Statistics for Drug Liking, Drug Liking AUE [0-1h], Drug Liking AUE [0- 2h], High, Overall Drug Liking and Take Drug Again, PD population (N=52)

Parameter	Treatment	Mean	Std Dev	Min	Q1	Median	Q3	Max
Drug Liking	A: INTACT OXYCODONE DETERX HFHC	76.04	17.19	50.00	60.50	79.50	91.50	100.00
	B: INTACT OXYCODONE DETERX FASTED	74.06	15.05	50.00	64.00	73.50	82.50	100.00
	C: CHEWED OXYCODONE DETERX HFHC	75.56	14.65	50.00	63.50	75.50	87.00	100.00
	D: CHEWED OXYCODONE DETERX FASTED	73.35	14.93	50.00	63.50	73.50	82.50	100.00
	E: CRUSHED IR OXYCODONE IN SOLUTION FASTED	86.40	12.00	52.00	77.50	88.50	97.00	100.00
	F: PLACEBO HFHC	55.83	9.93	50.00	50.00	50.00	59.00	86.00
High	A: INTACT OXYCODONE DETERX HFHC	44.44	33.03	0.00	11.50	43.00	78.00	100.00
	B: INTACT OXYCODONE DETERX FASTED	42.69	30.15	1.00	16.00	39.00	69.00	100.00
	C: CHEWED OXYCODONE DETERX HFHC	44.44	30.71	0.00	19.00	37.50	72.50	97.00
	D: CHEWED OXYCODONE DETERX FASTED	43.79	30.85	0.00	17.00	47.50	72.50	93.00
	E: CRUSHED IR OXYCODONE IN SOLUTION FASTED	73.87	26.08	3.00	64.50	81.00	93.50	100.00
	F: PLACEBO HFHC	9.65	18.05	0.00	0.00	0.00	14.50	76.00
Overall Drug Liking	A: INTACT OXYCODONE DETERX HFHC	77.46	17.51	50.00	64.50	78.50	94.00	100.00
	B: INTACT OXYCODONE DETERX FASTED	76.73	17.33	47.00	63.50	77.50	92.00	100.00
	C: CHEWED OXYCODONE DETERX HFHC	76.25	17.95	38.00	60.00	77.00	92.50	100.00
	D: CHEWED OXYCODONE DETERX FASTED	75.73	17.83	50.00	58.50	76.50	91.50	100.00
	E: CRUSHED IR OXYCODONE IN SOLUTION FASTED	86.52	12.41	50.00	80.00	87.00	100.00	100.00

Reference ID: 4177789

The following figures are from Dr. Sun's review.

Figure 1. Mean Drug Liking VAS Scores over time (PD Population, N=52)

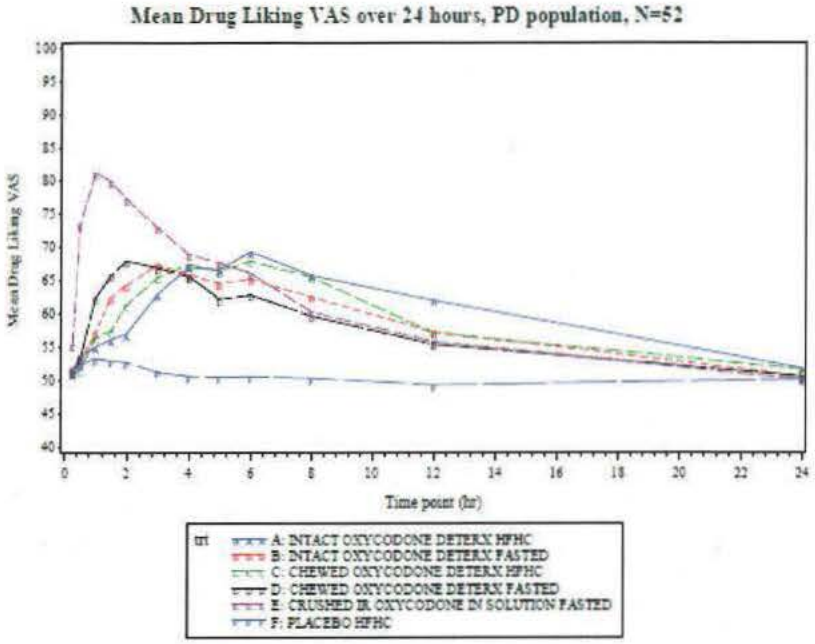
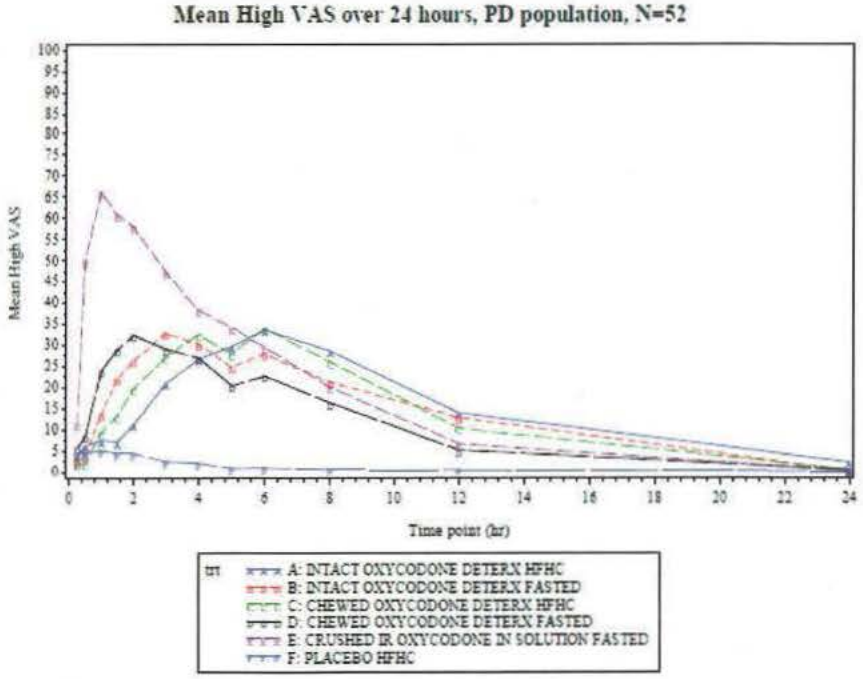


Figure 2. Mean High VAS Scores over time (PD Population, N=52)



Reference ID: 4177789

As noted by Dr. Sun, the High Emax, Overall Drug Liking Emax, and Take Drug Again Emax were all statistically significantly higher for crushed IR oxycodone fasted compared with chewed Xtampza fasted and fed ($p < 0.0001$, for each). These findings together with the pharmacokinetic data support labeling describing a deterrent effect for Xtampza when chewed and taken orally.

12. Labeling

The package insert was reviewed by the Division of Consumer Drug Promotion and suggested edits were incorporated into labeling.

The product labeling will include information about the results of the evaluation of abuse-deterrent properties of Xtampza, as described in the guidance[4], "When premarket data show that a product's abuse-deterrent properties can be expected to result in a meaningful reduction in that product's abuse, these data, together with an accurate characterization of what the data mean, should be included in product labeling." To provide an accurate characterization of the data from the evaluation of abuse-deterrent properties, results from the in vitro and in vivo studies will be included. Overall there is evidence that Xtampza can be expected to deter abuse by the intravenous route as characterized by results from the in vitro evaluation of syringeability, and by the oral and intranasal routes as characterized by the results of in vitro, pharmacokinetic, and abuse potential studies.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action –Approval
- Risk Benefit Assessment

In this supplemental application, the applicant has provided adequate pharmacokinetic and pharmacodynamic data to support a finding that Xtampza has properties that can be expected to deter oral abuse by chewing, although, abuse by the oral route is still possible. The additional pharmacokinetic data continue to support the finding that Xtampza is resistant to dose dumping when chewed or crushed, a safety advantage for Xtampza ER over other, currently approved extended-release oxycodone products that benefits the intended patient population.

A 30-month stay of approval of NDA 208090/Supplement 004 is not available based on Purdue Pharma L.P.'s patent infringement action against Collegium Pharmaceutical, Inc., that was initiated within 45 days of receiving notice of the paragraph IV certifications to U.S. Patent Nos. 9,522,919 (the '919 patent) and 9,073,933 (the '933 patent) on or about August 28, 2017, because information on the '919 and '933 patents was submitted to FDA after the date

[4] Abuse-Deterrent Opioids — Evaluation and Labeling, Guidance for Industry, http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf

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of submission of the original NDA 208090 for Xtampza ER (oxycodone) extended-release capsules (see section 505(c)(3)(C) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)).

- Recommendation for Postmarketing Risk Management Activities

Xtampza ER will be part of the Extended-release and Long-acting Opioid Analgesic REMS.

- Recommendation for other Postmarketing Study Commitments

There are no new postmarketing requirements from this supplemental NDA. The prior postmarketing requirements remain in effect.

Reference ID: 4177789

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/s/

SHARON H HERTZ
11/06/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 208090/S-004

PHARMACOLOGY REVIEW(S)

MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: September 29, 2017

To: Sharon Hertz, M.D., Director
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Through: Dominic Chiapperino, Ph.D., Acting Director
Silvia Calderon, Ph.D., Lead Pharmacologist
Controlled Substance Staff

From: James M. Tolliver, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: Xtampza ER (oxycodone) Extended-Release Capsules, NDA 208090, SN 0098
Supplement 4
Dosages, formulations, routes: Capsules for oral administration containing oxycodone base at dosage strengths 9.0 mg, 13.5 mg, 18 mg, 27 mg, and 36 mg. (Oxycodone HCl equivalents are 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg)
Indication(s): Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatments are inadequate.
Sponsor: Collegium Pharmaceutical Inc.
PDUFA Goal Date: November 3, 2017

Materials Reviewed:

Human abuse potential study CP-OXYDET-28 submitted to the Agency on March 24, 2017 under efficacy supplement 004 under NDA 208090.

Table of Contents

I. SUMMARY

1. Background

This memorandum responds to a consult request dated March 3, 2017, from the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) for CSS to evaluate oral human abuse potential study CP-OXYDET-28 entitled "Assessment of the Oral Human Abuse Liability and Pharmacokinetics of Oxycodone DETERx." This study was submitted to the Agency via letter dated March 24, 2017, from Collegium Pharmaceuticals under Supplement 004 of NDA 208090 SN0098 for Xtampza ER (oxycodone) Capsules, also known as Oxycodone DETERx. Study CP-OXYDET-28 is available in DARRTS (SN 0098).

NDA 208090 received FDA approval on April 26, 2016. Xtampza ER Capsules are intended for oral administration and contain oxycodone HCl salt in amounts that that give oxycodone base at dosage strengths 9.0 mg, 13.5 mg, 18 mg, 27 mg, and 36 mg (Oxycodone HCl equivalents are 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg). The drug product is indicated for management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatments are inadequate. Xtampza Capsules is in Schedule II of the federal Controlled Substances Act (CSA), as an oxycodone-containing drug product.

Under the original submission, the Sponsor conducted oral HAP study CP-OXYDET-25. In the "Summary Review for Regulatory Action" written by the Director of DAAAP (Dr. Hertz) (DARRTS, NDA 208090, Author: Sharon Hertz, M.D.) the following statement sums up the review of study CP-OXYDET-25:

> *The clinical abuse potential study that evaluated the abuse-deterrent properties of Xtampza ER for abuse by the oral route after chewing or crushing did not support a finding that Xtampza ER can be expected to deter oral abuse as there was no significant difference in the results of the outcome measure "take drug again". However, the pharmacokinetic data following oral administration of crushed or chewed Xtampza ER revealed that there was no increase in release of oxycodone compared to the intact state. This information is important with regard to patient safety, but alone cannot support a finding that Xtampza ER is likely to deter oral abuse. This will be conveyed in the labeling. To support such a finding, the Applicant must conduct an adequate and well controlled oral human abuse potential study.*

In response to the Action Regulatory Letter, the Sponsor conducted oral study CP-OXYDET-28, the subject of the current review. Throughout the study the test drug is referred to as Oxycodone DETERx.

2. Conclusions

1. Overall Conclusions: The pharmacokinetic and pharmacodynamic results of study CP-OXYDET-28 indicate that subjects chewing Oxycodone DETERx Capsules report lower "Drug Liking" and "Take Drug Again" scores than when taking IR Oxycodone HCl crushed tablets in solution.[1] Although these results indicate that DETERx capsules formulation may provide an abuse deterrent effect when chewed, the study results also indicate that ingestion of intact DETERx Capsules or the swallowing of chewed DETERx Capsules is still associated with some abuse potential, as described below, quantified based on measured subjective effects.

2. Evidence of a possible deterrent effect of Oxycodone DETERx to abuse by chewing comes from the following observations regarding the subjective measures of Drug Liking VAS, High VAS, Take Drug Again VAS, and Overall Drug Liking VAS,
    a. With respect to the primary comparisons for all four measures, oral administration of 40 mg crushed Oxycodone IR in solution (control) resulted in maximum peak effects (Emax) that were statistically higher ($p < 0.0001$) compared to following administration of chewed, followed by swallowing, 40 mg Oxycodone DETERx administered under either fed or fasted conductions. Due to the limited median differences observed in the nonparametric analysis of the Take Drug Again data, the clinical relevance of the observed differences with respect to Take Drug Again is not known. (See Tables 4, 5, 6, 7. 8, 9, 10, and 11 of Discussion)
    b. For all four measures, the mean Emax values following chewed 40 mg Oxycodone DETERx were similar to the mean Emax values achieved following oral intact 40 mg Oxycodone DETERx when the two treatments were administered under fed or fasted conditions. When compared to the intact Oxycodone DETERx formulation, chewing did not result in a compromise of the controlled release of oxycodone. (See Tables 4, 6, 8, and 10 of Discussion)

3. Intact as well as chewed 40 mg Oxycodone DETERx upon oral administration was associated with some abuse potential as evidenced by higher Emax values following these treatments on all four subjective measures compared to following placebo administration. (See Tables 4, 6, 8, and 10 of Discussion).

4. Oral administration of Oxycodone DETERx, whether intact or chewed, was associated with lower maximum oxycodone plasma concentrations (Cmax) compared to that observed following crushed Oxycodone IR in Solution. Likewise, oxycodone plasma Cmax were similar when comparing oral intact Oxycodone DETERx to chewed Oxycodone DETERx. These observations provide pharmacokinetic evidence for a predictive deterrent effect of Oxycodone DETERx to abuse by chewing. (See Table 3 of Discussion)

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[1] Throughout this review, all references to treatments administered "in solution" involve solutions of room temperature, non-carbonated water containing denatonium benzoate, a bittering agent intended to mask the bitterness of oxycodone-containing solutions versus placebo solutions.

3. Recommendations

Based on our findings as captured in the Conclusions section, we recommend the following:

1. The Division should consider, based on the findings for study CP-OXYDET-28, giving DETERx Capsules a deterrent claim to abuse by chewing. Both the pharmacokinetic and pharmacodynamic data support such a claim. Information regarding study CP-OXYDET-28 should be placed into Section 9.2 of the label for Oxycodone DETERx under the tradename of XTAMPZA ER Capsules. However, the label should clearly state that the formulation may still be orally abused either in its intact or manipulated form.

II. DISCUSSION

1. Chemistry

Xtampza ER Capsules, also known as Oxycodone DETERx is under development as an abuse-deterrent, oxycodone extended-release (ER) capsule oral formulation. It is manufactured in five strengths including 9 mg, 13.5 mg, 18 mg, 27 mg, and 36 mg oxycodone base. The oxycodone HCl equivalent for these strengths is 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg, respectively.

The Xtampza ER capsule formulation contains microspheres with a median particle size of approximately (b) (4) microns. The microspheres contain oxycodone base, myristic acid, yellow beeswax, carnauba wax, and stearoyl polyoxyl-32 glycerides. Microspheres are (b) (4) colloidal silicon dioxide and magnesium stearate to form (b) (4) (b) (4) in (b) (4) capsules (hypromellose hard shell capsules) to produce the final dosage form. The quantitative composition of the five dosage strengths for Xtampza ER capsules is provided in Table 1.

Table 1. Quantitative Composition of Xtampza ER Capsules (Source: Table 1 on pages 5 and 6 of Description and Composition of the Drug Product, Module 3.2.P.1)

Components	Dosage Strength (Oxycodone HCl Equivalent)				
	10 mg	15 mg	20 mg	30 mg	40 mg
	Quantity per Capsule (mg)				
Microspheres					
Oxycodone Base	(b) (4)				
Myristic Acid					
Yellow Beeswax					
Carnauba Wax					
Stearoyl Polyoxyl-32 Glycerides					
(b) (4)					
Microspheres (b) (4)					
	(b) (4)				
Magnesium Stearate	(b) (4)				
Colloidal Silicon Dioxide					
(b) (4)					

Hard Capsule Shell	
Hypromellose Capsule Shell	(b) (4)
Printing Ink	
(b) (4)	

1.3 In Vitro Manipulation and Extraction Studies for Products with Abuse-Deterrent Features

No new Category 1 physical manipulation or chemical extraction studies were submitted under Efficacy Supplement 004 for NDA 208090.

Under the original submission, Sponsor did provide a series to Category 1 studies. These studies were reviewed by CSS under the original submission (DAARTS, NDA 208090, September 9, 2015, Author: James M. Tolliver, Ph.D.).

4. Clinical Studies

4.1 Human Abuse Potential Studies

Study CP-OXYDET-28 is entitled "Assessment of the Oral Human Abuse Liability and Pharmacokinetics of Oxycodone DETERx." Study was conducted over the period of March-December 2016 by Vince and Associates Clinical Research, Overland Park, Kansas. Final study report is dated March 16, 2017.

The study design consisted of a randomized, double-blind, triple-dummy, active- and placebo-controlled, single-dose, 6-treatment, 6-period crossover comparison consisting of a Screening Phase, Drug Discrimination Phase, Double-blind Treatment Phase, and Follow-up Safety Phase.

The primary objective of this study was to evaluate the abuse liability and pharmacokinetics (PK) of oxycodone after intact and chewed oral administration of Oxycodone DETERx under fed (high-fat, high-calorie [HFHC]) and fasted conditions, and crushed immediate-release (IR) oxycodone under fasted conditions.

Subjects were non-dependent, recreational opioid users. A recreational opioid user is defined as a user of opioids for non-medical purposes (i.e., for psychoactive effects) on at least 10 occasions within the last year and at least once in the 12 weeks before the Screening Phase (Visit 1). Diagnosis of non-dependency and tolerance to opioids was based on DSM-V criteria and naloxone challenge.

Methodology – Drug Discrimination Phase

During the Drug Discrimination Phase subjects were required to complete a Naloxone Challenge Test and Drug Discrimination Test. Subjects who successfully completed the Naloxone Challenge Test remained as inpatients to complete the Drug Discrimination Test. In a two-way crossover, 1:1 ratio,

double-blind, randomized design, subjects received under fasted conditions a single, oral dose of the following treatments:

- Crushed IR Oxycodone HCl 40 mg Dosed Orally in Solution
- Placebo Dosed Orally Crushed, in Solution

For crushed IR oxycodone 40 mg, 2 oxycodone HCl 20 mg tablets were crushed and dissolved in 50 mL solution with room temperature, noncarbonated water, also containing denatonium benzoate, and administered orally. Placebo consisted of microcrystalline cellulose in 50 mL solution with room temperature, noncarbonated water and denatonium benzoate. The denatonium benzoate is in all solutions as a bittering agent to mask the bitter taste of oxycodone-containing solutions. Subjects were administered each test dose with 250 mL of room temperature, non-carbonatedwater.

In order to participate in the Treatment Phase, subjects were required to satisfy the following criteria in the Drug Discrimination Phase:

- A minimum (peak) effect (Emax) of at least 75 points for Drug Liking VAS in response to active treatment, IR oxycodone;
- A $\geq$ 15-point difference between IR oxycodone and placebo treatments at 1 or more time points following study drug administration;
- A placebo response $\geq$45 and $\leq$55 points for Drug Liking VAS following administration
- Must be able to tolerate study treatments in the Drug Discrimination Test as evidenced by no emesis within first 12 hours after dosing.

Methodology – Treatment Phase

During the Double-blind Treatment Phase, subjects were randomized, using a 6 x 6 Williams square randomization design, in a 1:1:1:1:1:1 ratio to receive a single dose of 6 treatments in a double-blind, triple-dummy crossover design. Each treatment was separated by a minimum of 5 days. Fed doses were administered following a "high fat high calorie" (HFHC) meal. Fasting doses were administered following an overnight fast lasting at least 10 hours. Any subject who could not finish his/her standardized HFHC breakfast in its entirety within 20 minutes (on fed dosing days) was not to be administered study drug and was discontinued from the study. Subjects received assigned dosages once in the morning. Treatments administered are shown in Table 6.

Table 2. Treatments Administered During Treatment Phase. (Active treatments are in bold type.)

Treatment	Chewed Capsule Contents	Intact Capsules	IR Solution	Fed/Fasted
A	DETERx Placebo	**Oxycodone DETERx 40 mg**	Placebo	HFHC
B	DETERx Placebo	**Oxycodone DETERx 40 mg**	Placebo	Fasted
C	**Oxycodone DETERx 40 mg**	DETERx Placebo	Placebo	HFHC
D	**Oxycodone DETERx 40 mg**	DETERx Placebo	Placebo	Fasted
E	DETERx Placebo	DETERx Placebo	**IR Oxycodone HCl 40 mg**	Fasted
F	DEERx Placebo	DETERx Placebo	Placebo	HFHC

A single 36 mg capsule (each equivalent to 40 mg of oxycodone hydrochloride) was used for each Oxycodone DETERx treatment. For IR oxycodone 40 mg, 2 oxycodone HCl 20 mg tablets were crushed and dissolved in 50 mL solution and administered orally. Placebo DETERx capsules, supplied by Sponsor were administered orally (intact or chewed) under fasted and fed conditions. Microcrystalline cellulose powder in 50 mL solution for oral administration served as the IR solution placebo treatment.

Subjects ingested intact capsules directly from a dosing container, assisted with 50 mL of IR oxycodone/placebo solution (room temperature, non-carbonated water with denatonium benzoate), followed by 1 rinse of 10 mL room temperature, non-carbonated water and an additional approximately 90 mL of room temperature, non-carbonated water to complete this step of dosing. For chewed capsules, subjects received the study drug capsule contents in a dosing cup and were instructed to pour the contents onto their tongue and tap the bottom of the dosing cup several times to deposit any remaining microspheres into their mouth. Subjects were instructed to chew the study drug capsule contents for 2 minutes, and were instructed not to swallow or talk while chewing the contents. Following chewing, 2 additional 50 mL rinses of room temperature, non-carbonated water were administered from the dosing container.

All study products were administered under supervision of the study personnel; ingestion (of intact capsules and chewed capsule contents) was verified by visual inspection of the mouth immediately following dosing.

Methodology – Pharmacokinetics of Oxycodone in Plasma – Treatment Phase

During each Treatment Period of the Double-blind Treatment Phase, serial 3 mL blood samples for pharmacokinetic evaluation were collected pre-dose and at 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 12.0, 24.0, and 36.0 hours post-dose. For purposes of this review, the PK parameters determined and reviewed for oxycodone were:

- C_{max} = Maximum plasma level of oxycodone achieved
- T_{max} = Time to achieve C_{max}
- AUC_{inf} = Area under the plasma oxycodone concentration versus time curve from time 0 extrapolated to infinity.

Methodology – Pharmacodynamic Assessments – Treatment Phase

For purposes of this review, the pharmacodynamic (PD) measures to be examined were bipolar Drug Liking VAS, Unipolar High VAS, Bipolar Take Drug Again VAS, and bipolar Overall Drug Liking VAS. The primary pharmacodynamic measure was Drug Liking VAS while the primary endpoint was maximum (peak) Drug Liking designated Emax. Secondary outcome measures included High VAS, Take Drug Again VAS and Overall Drug Liking VAS. Drug Liking VAS and High VAS were conducted at 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 12.0 and 24.0 hours post-dosing. Bipolar Take Drug Again VAS was conducted at 8 hours and 24 hours post-dosing.

For purposes of the review, the pharmacodynamic endpoints of interest will include:

- Emax = Maximum observed effect
- TEmax = Time to Achieve Emax

- AUE0-2hrs = Area under the effect curve from 0 hours to 2 hours post-dosing.

Results – Subject Disposition

A total of 174 subjects entered the Drug Discrimination Phase, passed the Naloxone Challenge Test, and received at least one study drug dose in the Drug Discrimination Test; these subjects comprised the Drug Discrimination Safety Population. A total of 75 subjects passed the Drug Discrimination Test and entered the Double-blind Treatment Phase. The 75 subjects who entered the Double-blind Treatment Phase represent the Safety Population, of which 71 subjects had sufficient PK data and represent the PK Population. A total of 52 subjects completed the study and comprise the PD Population.

Results – Pharmacokinetics of Plasma Oxycodone Following Active Treatments

Pharmacokinetic parameters for plasma oxycodone following active treatments is provided in Table 3 below. Oral administration of Oxycodone IR Solution (comparator) was associated with an approximately 2 fold increase of maximum plasma oxycodone concentration (Cmax) compared to following oral administration of Oxycodone DETERx, intact or ground, under fed conditions. Likewise, the Cmax of plasma oxycodone was approximately 2.5 to 2.8 fold lower following either intact or chewed Oxycodone DETERx under fasted conditions compared to that resulting from Oxycodone IR oral solutions. So oral administration of Oxycodone DETERx, whether intact or chewed, was associated with lower oxycodone plasma concentrations compared to crushed Oxycodone IR in Solutions.

In addition, oxycodone plasma Tmax was shorter following oral crushed IR Oxycodone (mean Tmax of 1.16 hours) in solution compared to that seen following oral administration of Oxycodone DETERx, intact or chewed, under fasted or fed conditions (mean Tmax ranging from 2.30 hours to 6.06 hours).

Table 3. Pharmacokinetic of Oxycodone in Plasma Observed during the Treatment Phase in the Pharmacodynamic Population (N=52). (Data Source: Listing 10 entitled "Descriptive Statistics for Oxycodone Pharmacokinetic Parameters – PD Population" on page 277 of the Pharmacokinetic and Statistical Report for Study CP-OXYDET-28).

Oxycodone Plasma PK Parameter	Statistic	Pharmacodynamic Population (N = 52)				
		Treatment A Intact Oxycodone DETERx HFHC	Treatment B Intact Oxycodone DETERx Fasted	Treatment C Chewed Oxycodone DETERx HFHC	Treatment D Chewed Oxycodone DETERX Fasted	Treatment E Crushed IR Oxycodone in Solution Fasted
Cmax (ng/mL)	Mean (SD)	46.223 (10.558)	32.429 (7.930)	43.581 (9.920)	36.942 (11.677)	92.640 (26.421)
Tmax (hrs)	Mean (SD)	6.06 (2.38)	3.56 (1.47)	4.85 (1.46)	2.30 (1.83)	1.16 (1.31)
	Median	5.05	3.07	5.07	2.57	0.53
	Range	2.07 – 12.07	1.52 – 8.07	1.52 – 8.07	0.53 – 8.07	0.30 – 5.15
AUCinf (hrs x ng/mL)	Mean (SD)	540.691 (126.420)	455.978 (112.890)	569.891 (130.169)	471.595 (130.907)	547.395 (135.884)

Results – Pharmacodynamics

For purposes of this review, the pharmacodynamic measures of interest were bipolar Drug Liking VAS, unipolar High VAS, bipolar Take Drug Again VAS, and bipolar Overall Drug Liking VAS.

Descriptive and inferential statistics for Emax of Drug Liking VAS, High VAS, Take Drug Again VAS, and Overall Drug Liking VAS were conducted by the CDER Office of Biostatistics. The final statistical report is available in DARRTS (NDA 208090, August 17, 2017, Author: Anna Sun, Ph.D.). For Drug Liking VAS, High VAS, and Overall Drug Liking VAS, the normality assumption tests were met, thereby allowing statistical analyses based on a mixed-effect model, with period, sequence, and treatment as fixed effects, and subjects nested within treatment sequence as a random effect. For Take Drug Again VAS, the normality assumption test was not met, thereby requiring use of a non-parametric method utilizing median values for Emax of Drug Liking.

Results – Drug Liking VAS

For assessing Drug Liking, subjects were asked the question "Do you like the effect that you are feeling now?" The question was scored using a 0-100 mm bipolar VAS anchored on the left with "strong disliking" (score of 0 mm); "neither like nor dislike" (score of 50 mm) in the middle; and anchored on the right with "strong liking" (score of 100 mm). Descriptive statistics for Emax of Drug Liking VAS is shown in Table 4. Statistical analyses of treatment differences are provided in Table 5.

Oral administration of crushed 40 mg Oxycodone IR Solutions produced an Emax of Drug Liking VAS (86.40 mm) that was statistically significantly higher ($p < 0.0001$) than that produced by placebo (55.83 mm), thereby validating the Drug Liking VAS measure.

Table 4. Descriptive Statistics for Emax of Drug Liking VAS in the Pharmacodynamic Population (N = 52) (Source: CDER Office of Biostatistics)

VAS	Treatment	Mean Emax (mm)	Standard Deviation	Minimum	First Quatrile	Median	Third Quatrile	Maximum
Drug Liking	A: Intact 40 mg Oxycodone DETERx HFHC	76.04	17.19	50.00	60.50	79.50	91.50	100.00
	B: Intact 40 mg Oxycodone DETERx Fasted	74.06	15.05	50.00	64.00	73.50	82.50	100.00
	C: Chewed 40 mg Oxycodone DETERx HFHC	75.56	14.65	50.00	63.50	75.50	87.00	100.00
	D: Chewed 40 mgOxycodone DETERx Fasted	73.35	14.93	50.00	63.50	73.50	82.50	100.00
	E: Crushed 40 mg Oxycodone IR Solution	86.40	12.00	52.00	77.50	88.50	97.00	100.00
	F: Placebo HFHC	55.83	9.93	50.00	50.00	50.00	59.00	86.00

With respect to primary comparisons, crushed 40 mg oxycodone IR solution resulted in a mean Emax of Drug Liking VAS (86.40 mm) that was statistically significantly higher ($p < 0.0001$) than that produced by chewed 40 mg Oxycodone DETERx administered under HFHC (75.56 mm) or fasted (73.35 mm) conditions. The time to achieve Emax (TEmax) was earliest for crushed IR oxycodone fasted (mean=1.92 hour, median=1.0 hour), followed by chewed Oxycodone DETERx fasted treatment

(mean=2.38 hour, median=2.0 hour), and latest for chewed Oxycodone DETERx HFHC treatment (mean=4.67 hour, median=4.0 hour).

The mean Emax values of Drug Liking VAS produced by intact and chewed Oxycodone DETERx under fasted or fed conditions, were similar with a range of 73.35 to 76.04 mm and were substantially above that of placebo (55.83 mm).

These data suggest that Oxycodone DETERx provides a deterrent effect to chewing. The data also indicate that Oxycodone DETERx whether ingested intact or chewed followed by swallowing is still associated with an abuse potential, when compared to placebo.

Table 5. Statistical Analyses of the Mean Difference in Emax for Drug Liking VAS, Pharmacodynamic Population (N = 52) (Source: CDER Office of Biostatistics)

Drug Liking VAS	LS Mean Emax	Standard Error	Pr > |t|	Lower Confidence Interval	Upper Confidence Internal
Treatments					
A: Intact 40 mg Oxycodone DETERx HFHC	76.50	1.93	<.0001	72.70	80.30
B: Intact 40 mg Oxycodone DETERx Fasted	74.57	1.93	<.0001	70.77	78.37
C: Chewed 40 mg Oxycodone DETERx HFHC	75.87	1.93	<.0001	72.07	79.67
D: Chewed 40 mg Oxycodone DETERx Fasted	73.71	1.93	<.0001	69.91	77.51
E: Crushed 40 mg Oxycodone IR Solution Fasted	86.80	1.93	<.0001	83.00	90.60
F: Placebo HFHC	56.14	1.93	<.0001	52.34	59.94
Contrasts (difference)					
E v F (Validation)	30.67	2.22	<.0001	26.29	35.05
E v D (Primary)	13.10	2.22	<.0001	8.72	17.48
E v C (Primary)	10.93	2.23	<.0001	6.54	15.32

Results – High VAS

For assessing High VAS, subjects were asked the question "How high are you now?" Subjects were required to mark a vertical line on a unipolar 0-100 mm VAS anchored on the left by "none" (score of 0) and on the right by "extremely" (score of 100). Descriptive statistics for Emax of High VAS is shown in Table 6. Statistical analyses of treatment differences are provided in Table 7.

Oral administration of crushed 40 mg Oxycodone IR Solutions produced an Emax of High VAS (73.87 mm) that was statistically significantly higher ($p < 0.0001$) than that produced by placebo (9.65 mm), thereby validating the High VAS measure.

Table 6. Descriptive Statistics for Emax of High VAS in the Pharmacodynamic Population (N = 52) (Source: CDER Office of Biostatistics)

VAS	Treatment	Mean Emax (mm)	Standard Deviation	Minimum	First Quatrile	Median	Third Quatrile	Maximum
High	A: Intact 40 mg Oxycodone DETERx HFHC	44.44	33.03	0.00	11.50	43.00	78.00	100.00
	B: Intact 40 mg Oxycodone DETERx Fasted	42.69	30.15	1.00	16.00	39.00	69.00	100.00
	C: Chewed 40 mg Oxycodone DETERx HFHC	44.44	30.71	0.00	19.00	37.50	72.50	97.00

	D: Chewed 40 mg Oxycodone DETERx Fasted	43.79	30.85	0.00	17.00	47.50	72.50	93.00
	E: Crushed 40 mg Oxycodone IR Solution Fasted	73.87	26.08	3.00	64.50	81.00	93.50	100.00
	F: Placebo HFHC	9.65	18.05	0.00	0.00	0.00	14.50	76.00

With respect to primary comparisons, crushed 40 mg oxycodone IR solution resulted in a mean Emax of High VAS (73.87 mm) that was statistically significantly higher ($p < 0.0001$) than that produced by chewed 40 mg Oxycodone DETERx administered under HFHC (44.44 mm) or fasted (43.79 mm) conditions. Chewed Oxycodone DETERx HFHC treatment had TEmax (mean=4.4 hour, median=4.0 hour) longer than the TEmax of chewed Oxycodone DETERx fasted treatment (mean=2.91 hour, median=2.0 hour) and for crushed IR oxycodone fasted (mean=1.60 hour, median=1.0 hour).

The mean Emax values of High VAS produced by intact and chewed Oxycodone DETERx under fasted or fed conditions, were similar with a range of 42.69 to 44.44 mm and were substantially above that of placebo.

These data suggest that Oxycodone DETERx provide a deterrent effect to chewing. At the same time, the data indicate that Oxycodone DETERx whether ingested intact or chewed followed by swallowing is still associated with an abuse potential, when compared to placebo.

Table 7. Statistical Analyses of the Mean Difference in Emax for High VAS, Pharmacodynamic Population (N = 52) (Source: CDER Office of Biostatistics)

	LS Mean Emax	**Standard Error**	**Pr > |t|**	**Lower Confidence Interval**	**Upper Confidence Interval**
Treatments					
A: Intact 40 mg Oxycodone DETERx HFHC	45.22	3.91	<.0001	37.51	52.93
B: Intact 40 mg Oxycodone DETERx Fasted	43.73	3.91	<.0001	36.02	51.43
C: Chewed 40 mg Oxycodone DETERx HFHC	45.26	3.91	<.0001	37.55	52.97
D: Chewed 40 mg Oxycodone DETERx Fasted	44.58	3.91	<.0001	36.87	52.29
E: Crushed 40 mg Oxycodone IR Solution Fasted	74.71	3.91	<.0001	67.00	82.42
F: Placebo HFHC	10.28	3.91	0.01	2.57	17.99
Contrasts (difference)					
E v F (Validation)	64.4	4.1	<.0001	56.3	72.5
E v D (Primary)	30.1	4.1	<.0001	22.0	38.2
E v C (Primary)	29.4	4.1	<.0001	21.3	37.6

Results – Take Drug Again VAS

The Take Drug Again VAS was intended to assess each subject's desire to use the drug again. This assessment involved asking subjects the question, "Would you want to take the drug you just received again, if given the opportunity?" The question was scored using a 0-100 mm bipolar VAS anchored on the left with "definitely would not" (score of 0); "do not care" (score of 50) in the middle; and anchored on the right with "definitely would" (score of 100). Descriptive statistics for Emax of Take Drug Again VAS is shown in Table 8. Non-parametric analyses of treatment differences are provided in Table 9.

Oral administration of crushed 40 mg Oxycodone IR Solutions produced an Emax of Take Drug Again VAS (87.69 mm) that was statistically significantly higher ($p < 0.0001$) than that produced by placebo (50.79 mm), thereby validating the Take Drug Again measure.

Table 8. Descriptive Statistics for Emax of Take Drug Again VAS in the Pharmacodynamic Population (N = 52) (Source: CDER Office of Biostatistics)

VAS	Treatment	Mean Emax (mm)	Standard Deviation	Minimum	First Quatrile	Median	Third Quatrile	Maximum
Take Drug Again	A: Intact 40 mg Oxycodone DETERx HFHC	78.17	21.18	0.00	61.50	81.00	100.00	100.00
	B: Intact 40 mg Oxycodone DETERx Fasted	77.98	21.07	1.00	64.50	80.50	100.00	100.00
	C: Chewed 40 mg Oxycodone DETERx HFHC	77.81	17.69	23.00	68.00	78.00	96.00	100.00
	D: Chewed 40 mg Oxycodone DETERx Fasted	77.85	18.30	50.00	62.00	81.50	96.50	100.00
	E: Crushed 40 mg Oxycodone IR Solution Fasted	87.69	12.90	50.00	81.00	90.50	100.00	100.00
	F: Placebo HFHC	50.79	21.41	0.00	50.00	50.00	50.50	100.00

Based upon nonparametric analysis as shown in Table 9, with respect to primary comparisons, crushed 40 mg oxycodone IR solution resulted in a mean Emax of Take Drug Again (87.69 mm) that was statistically significantly higher ($p < 0.0001$) than that produced by chewed 40 mg Oxycodone DETERx administered under HFHC (77.81 mm) or fasted (77.85 mm) conditions. Based on the limited median differences (4.50 and 3.50) the clinical relevance of these differences is not clear.

Mean Emax for Take Drug Again were similar between intact and chewed Oxycodone DETERx administered under fed or fasted conditions (range of 77.81 mm to 78.17 mm). Data demonstrate that the product still has an oral abuse potential, as evidenced from comparison with placebo administration (77.81 to 78.17 mm compared to 50. 79 mm for placebo).

Table 9. Nonparametric Analyses of Take Drug Again Exam in the Pharmacodynamic Population (N=52) (Source: CDER Office of Biostatistics)

Treatment Difference	**Median Difference**	**Standard Error**	**Interquartile Range**	**P-value**
E v F (Validation)	39.5	25.94	31	<.0001
E v D (Primary)	4.50	17.00	19.5	<.0001
E v C (Primary)	3.50	17.71	18	<.0001

Results – Overall (Global) Drug Liking VAS

The Overall Drug Liking VAS was intended to assess the subject's global perception of drug liking (i.e., the subjective effects over the whole course of the drug experience including any carryover effects). The question was scored using a 100-point bipolar VAS anchored on the left with "strong disliking" (0 points); "neither like nor dislike" (50 points) in the middle; and anchored on the right with "strong

liking" (100 points). Descriptive statistics for Emax of Take Drug Again VAS is shown in Table 10. Statistical analyses of treatment differences are provided in Table 11.

Oral administration of crushed 40 mg Oxycodone IR Solutions produced an Emax of Overall Drug Liking VAS (86.52 mm) that was statistically significantly higher ($p < 0.0001$) than that produced by placebo (55.46 mm), thereby validating the Overall Drug Liking measure.

Table 10. Descriptive Statistics for Emax of Overall Drug Liking VAS in the Pharmacodynamic Population (N = 52). (Source: CDER Office of Biostatistics)

VAS	Treatment	Mean Emax (mm)	Standard Deviation	Minimum	First Quatrile	Median	Third Quatrile	Maximum
Overall Drug Liking	A: Intact 40 mg Oxycodone DETERx HFHC	77.46	17.51	50.00	64.50	78.50	94.00	100.00
	B: Intact 40 mg Oxycodone DETERx Fasted	76.73	17.33	47.00	63.50	77.50	92.00	100.00
	C: Chewed 40 mg Oxycodone DETERx HFHC	76.25	17.95	38.00	60.00	77.00	92.50	100.00
	D: Chewed 40 mg Oxycodone DETERx Fasted	75.73	17.83	50.00	58.50	76.50	91.50	100.00
	E: Crushed 40 mg Oxycodone IR Solution Fasted	86.52	12.41	50.00	80.00	87.00	100.00	100.00
	F: Placebo HFHC	55.46	13.05	50.00	50.00	50.00	51.00	100.00

With respect to primary comparisons, crushed 40 mg oxycodone IR solution resulted in a mean Emax of Overall Drug Liking (86.52 mm) that was statistically significantly higher than that produced by chewed 40 mg Oxycodone DETERx administered under HFHC (76.25 mm) or fasted (75.73 mm) conditions. These results demonstrate an abuse deterrent effect of Oxycodone DETERx to chewing compared to oral intact administration.

Table 11. Statistical Analyses of the Mean Difference in Emax for Overall Drug Liking VAS, Pharmacodynamic Population (N = 52) (Source: CDER Office of Biostatistics)

	LS Mean Emax	**Standard Error**	**Pr > |t|**	**Lower Confidence Interval**	**Upper Confidence Interval**
Treatments					
A: Intact 40 mg Oxycodone DETERx HFHC	78.05	2.24	<.0001	73.64	82.47
B: Intact 40 mg Oxycodone DETERx Fasted	77.32	2.24	<.0001	72.90	81.74
C: Chewed 40 mg Oxycodone DETERx HFHC	76.61	2.24	<.0001	72.19	81.02
D: Chewed 40 mg Oxycodone DETERx Fasted	76.02	2.24	<.0001	71.60	80.43
E: Crushed 40 mg Oxycodone IR Solution Fasted	86.92	2.24	<.0001	82.51	91.34
F: Placebo HFHC	55.94	2.24	0.01	51.53	60.36
Contrasts (difference)					
E v F (Validation)	30.98	2.52	<.0001	26.02	35.94
E v D (Primary)	10.91	2.52	<.0001	5.95	15.87
E v C (Primary)	10.32	2.52	<.0001	5.34	15.29

The Overall Drug Liking produced by oral Oxycodone DETERx did not vary depending on fed and fasted condition. In addition, with comparison of chewed versus oral intact Oxycodone DETERx, similar mean Emax of Overall Drug Liking VAS were observed (range 75.73 mm to 77.46 mm).

However, with mean Emax of Overall Drug Liking in the range of 75 mm to 77 mm, there does appear to be an abuse potential associated with oral intact or chewed Oxycodone DETERx administered under fed or fasted conditions.

Overall Conclusions from Study CP-OXYDET-28

The pharmacokinetic and pharmacodynamic results of study CP-OXYDET-28 indicate that Oxycodone DETERx Capsules, provide an abuse deterrent effect when chewed. In addition, the results indicate that ingestion of intact DETERx Capsules or chewing followed by swallowing of DETERx Capsules is associated with an abuse potential.

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/s/

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 208090/S-004

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

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Drug Name:	Oxycodone DETERx
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Study number:	CP-OXYDET-28
Applicant:	Collegium Pharmaceutical, Inc.
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Statistical Reviewer:	Anna Sun, Ph.D., Mathematical Statistician, OB/DBVI
Concurring Reviewers:	Qianyu Dang, Ph.D., Lead Mathematical Statistician, OB/DBVI Yi Tsong, Ph.D., Division Director, OB/DBVI
Medical Division:	Control Substance Staff
The CSS Team:	James Tolliver, Ph.D., Pharmacologist, OCD/CSS
Project Manager:	Sandra Saltz, Project Manager, CSS

Keywords: *Crossover design, Drug abuse potential study, Self-reported endpoint, Multiple endpoints*

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1. Executive Summary

Study CP-OXYDET-28 was a randomized, double-blind, triple-dummy, active- and placebo-controlled, single-dose, 6-treatment, 6-period crossover comparison study designed to evaluate the oral abuse liability and PK of intact and chewed Oxycodone DETERx under fed (HFHC) and fasted conditions compared with crushed IR oxycodone under fasted conditions.

The primary objective of this study was to evaluate the abuse liability and PK of oxycodone after intact and chewed oral administration of Oxycodone DETERx under fed (high-fat, high-calorie [HFHC]) and fasted conditions, and crushed IR oxycodone under fasted conditions.

The primary PD outcome measure was Drug Liking from the DEQ; the primary endpoint was Drug Liking Emax. The secondary outcome measures were: feeling high, any drug effects, good effects, bad effects, feel sick, nausea, sleepy, and dizzy from the DEQ; Overall (Global) Drug Liking; ARCI/MBG; Take Drug Again Assessment; PVAQ; and pupillometry. There were six treatments in the study, the primary comparisons were Treatment E (crushed IR oxycodone fasted) versus Treatment D (chewed Oxycodone DETERx fasted, and Treatment E (crushed IR oxycodone fasted) versus Treatment C (chewed Oxycodone DETERx HFHC.

The reviewer analyzed the primary PD endpoint Drug Liking, and the secondary PD endpoints: Drug Liking AUE [0-1h] Emax, Drug Liking AUE [0-2h] Emax, High, Take Drug Again and Overall Drug Liking. The results from the statistical reviewer's analyses establish that:

- The Crushed IR Oxycodone Fasted resulted in statistically significantly greater ($p<0.0001$) VAS scores compared to Placebo HFHC for Drug Liking, High, Take Drug Again and Overall Drug Liking, thereby validating these pharmacodynamic measures.

- The LS mean (95% CI) Emax for Drug Liking for chewed Oxycodone DETERx fasted and for chewed Oxycodone DETERx HFHC were 73.71 (69.91, 77.51) and 75.87 (72.07, 79.67), respectively, compared with 86.80 (83.00, 90.60) for crushed IR oxycodone fasted. The LS mean (95% CI) differences were 13.10 (8.72, 17.48) and 10.93 (6.54, 15.32), respectively, both comparisons showed that the differences were statistically significant ($P<0.0001$).

- High Emax was statistically significantly higher for crushed IR oxycodone fasted compared with chewed Oxycodone DETERx fasted and HFHC ($p < 0.0001$).

- Overall Drug Liking Emax was statistically significantly higher for crushed IR oxycodone fasted compared with chewed Oxycodone DETERx fasted and HFHC ($p < 0.0001$.

- Take Drug Again Emax was statistically significantly higher for crushed IR oxycodone fasted compared with chewed Oxycodone DETERx fasted and HFHC ($p < 0.0001$).

- 40 out of the 52 subjects who completed the study (~77%) had some reduction in Drug Liking with Chewed Oxycodone DETERx Fasted (Treatment D) compare to Crushed IR Oxycodone Fasted (Treatment E). 26 subjects (50%) experienced at least a 30% reduction and 18 subjects (~35%) had at least a 50% reduction in Emax of Drug Liking with Chewed Oxycodone DETERx Fasted (Treatment D) compare to Crushed IR Oxycodone Fasted (Treatment E).

- 38 out of the 52 subjects who completed the study (~73%) had some reduction in Drug Liking with Chewed Oxycodone DETERx HFHC (Treatment C) versus Crushed IR

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Oxycodone Fasted (Treatment E). 20 subjects (~38%) experienced at least a 30% reduction and 14 subjects (~27%) had at least a 50% reduction in Emax of Drug Liking with Chewed Oxycodone DETERx HFHC (Treatment C) versus Crushed IR Oxycodone Fasted (Treatment E).

By following the 2015 new guidance:

- Emax of Crushed IR Oxycodone Fasted is significantly greater than Placebo HFHC (P<0.0001) for Drug Liking VAS, High VAS and Overall Drug Liking VAS, thereby confirming study validity.

- For the primary comparison between E: Crushed IR Oxycodone Fasted vs. D: Chewed Oxycodone DETERx Fasted, D: Chewed Oxycodone DETERx Fasted had statistically significant 20% reduction in Emax of Drug Liking VAS, 30% reduction in Emax of High VAS, and 15% reduction in Emax of Overall Drug Liking VAS comparing with E: Crushed IR Oxycodone Fasted.

- For the primary comparison between E: Crushed IR Oxycodone Fasted vs. C: Chewed Oxycodone DETERx HFHC, C: Chewed Oxycodone DETERx HFHC had statistically significant 15% reduction in Emax of Drug Liking VAS, 25% reduction in Emax of High VAS, and 15% reduction in Emax of Overall Drug Liking VAS comparing with E: Crushed IR Oxycodone Fasted.

Additional comments

1. On page 89 of the Clinical Study Report, Table 9 shows Inferential Analysis for Drug Liking Emax for Primary Comparison, in the footnote, sponsored mentioned 'T was statistically lower than C by > 7.4 or 5.5 points, respectively, using d* = 0.20 or 0.15, respectively, the last value prior to non-significance;'

   Reviewer's comments: For the hypothesis testing,

   $H_0 : \mu_C - \mu_T \le (\mu_C - 50)\delta^* \; vs \; H_a : \mu_C - \mu_T > (\mu_C - 50)\delta^*$

   μ_C is unknown, you should not use the least square mean of control to replace μ_C. Instead, you may test following hypothesis which is equivalent to above but only need to specify δ^*:

   $H_0 : \mu_T - (1-\delta^*)\mu_C \ge 50\delta^* \; vs \; H_a : \mu_T - (1-\delta^*)\mu_C < 50\delta^*$

2. As to the percent reduction profile plot, you should use >0 instead of ≥0 for the first data point.

2. Review Report on Study CP-OXYDET-28

2.1 Overview

The misuse and abuse of opioid medications, including oxycodone, continues to increase precipitously. Extended-release (ER) formulations of opioids contain high doses of active drug in order to maintain the analgesic effect over a prolonged dosing interval. Abusers frequently tamper with these formulations in an attempt to subvert the time-release mechanism and access the entire drug load at once. Many conventional ER formulations are susceptible to tampering techniques such as breaking, crushing, or chewing. Chewing ER formulations is done to circumvent the ER mechanism and, thereby, achieve euphoric effects rapidly. Due to concerns about the diversion

and abuse of pharmaceutical opioids, various formulations have been developed to deter the nonmedical use of the medication.

The Sponsor has developed the Oxycodone DETERx (Xtampza® ER) formulation to provide clinicians and patients with a tamper-resistant version of the drug in the form of an ER oxycodone preparation. The Oxycodone DETERx formulation, which contains pharmaceutically-active microspheres delivered in a capsule for oral administration, has been developed to provide clinicians and patients with a novel abuse-deterrent formulation of oxycodone. Data from the oral PK studies (CP-OXYDET-17, CP-OXYDET-25, CP-OXYDET-27, and CP-OXYDET-29) of manipulated Oxycodone DETERx demonstrated a lack of dose dumping with no increase in oxycodone levels compared to intact Oxycodone DETERx, and although the results of the pivotal oral human abuse liability study (CP-OXYDET-24) showed a robust difference in the Drug Liking maximum effect (Emax) endpoint between Oxycodone DETERx 40 mg and the active control, immediate-release (IR) oxycodone 40 mg, there was no statistically significant reduction in the response to the Take Drug Again visual analog scale (VAS). Therefore, this study was conducted with modification relative to study CP-OXYDET-24, including selection of subjects during the Drug Discrimination Test based on their responses to IR oxycodone 40 mg.

The purpose of this study was to comparatively assess the oral human abuse liability and the plasma concentrations of oxycodone following per os (PO) administration of Oxycodone DETERx intact and chewed compared with PO administration of crushed IR oxycodone (fasted) and placebo in nondependent, recreational opioid users. Because Oxycodone DETERx has a known food effect, the oral abuse liability of Oxycodone DETERx 40 mg (intact and chewed) was studied in both the fed and fasted states.

2.1.1 Objectives of the study

The primary objective of this study was to evaluate the abuse liability and PK of oxycodone after intact and chewed oral administration of Oxycodone DETERx under fed (high-fat, high-calorie [HFHC]) and fasted conditions, and crushed IR oxycodone under fasted conditions.

2.1.2 Study design

This was a randomized, double-blind, triple-dummy, active- and placebo-controlled, single-dose, 6-treatment, 6-period crossover comparison study designed to evaluate the oral abuse liability and PK of intact and chewed Oxycodone DETERx under fed (HFHC) and fasted conditions compared with crushed IR oxycodone under fasted conditions.

There were 4 study phases: Screening Phase, Drug Discrimination Phase, Double-blind Treatment Phase, and Follow-up Safety Phase.

Subjects who successfully completed the Screening Phase (Visit 1) returned to the clinical research unit as inpatients to complete the Drug Discrimination Phase. The Drug Discrimination Phase comprised a Naloxone Challenge Test to confirm that subjects were not opioid tolerant and a Drug Discrimination Test to ensure that subjects could differentiate between the effects of a single 40 mg dose of crushed IR oxycodone and placebo in oral solution.

Subjects who successfully completed the Naloxone Challenge Test remained as inpatients to complete the Drug Discrimination Test. In the Drug Discrimination Test, subjects were randomized in a 1:1 ratio to receive a single, PO dose of each of the following treatments in a double-blind crossover manner under fasted conditions:

• Crushed IR oxycodone 40 mg, in solution

• Placebo powder, in solution

Each dose was separated by at least 24 hours. Subjects were discharged from the clinical research unit approximately 24 hours after the second dose, if deemed safe by the Investigator. Subjects who were eligible to continue the study returned to the clinical research unit to begin the Double-blind Treatment Phase. A period of 5 to 21 days separated the second treatment in the Drug Discrimination Test and the first treatment in the Double-blind Treatment Phase.

During the Double-blind Treatment Phase, subjects were randomized in a 1:1:1:1:1:1 ratio to receive a single dose of each of the following 6 treatments in a double-blind, triple-dummy (chewed capsule, intact capsule, solution) crossover manner (1 per Treatment Period):

Treatment	Chewed	Intact Capsule	IR Solution	Fed/Fasted
A	DETERx placebo	**Oxycodone DETERx**	Placebo	HFHC
B	DETERx placebo	**Oxycodone DETERx**	Placebo	Fasted
C	**Oxycodone DETERx**	DETERx placebo	Placebo	HFHC
D	**Oxycodone DETERx**	DETERx placebo	Placebo	Fasted
E	DETERx placebo	DETERx placebo	**IR oxycodone**	Fasted
F	DETERx placebo	DETERx placebo	Placebo	HFHC

HFHC=high-fat, high-calorie; IR=immediate-release. Active treatments (each dose equivalent to 40 mg of oxycodone hydrochloride) are in bold.

For all Treatment Periods, subjects remained in the clinic until approximately 36 hours after dosing. Subjects were only discharged if the Investigator deemed it was safe; subjects could be asked to reside in the clinical research unit for a longer period of time, if necessary. Each treatment was separated by a period of 5 to 21 days.

Subjects who enrolled into the Double-blind Treatment Phase were to be contacted via phone approximately 5 (± 2) days following discharge from the Double-blind Treatment Phase or after early discontinuation from the study for a Safety Follow-up Visit.

Pharmacodynamic Endpoints:

The primary PD outcome measure was Drug Liking from the DEQ; the primary endpoint was Drug Liking Emax during the 8 hours after dosing. The secondary outcome measures were: feeling high, any drug effects, good effects, bad effects, feel sick, nausea, sleepy, and dizzy from the DEQ; Overall (Global) Drug Liking; ARCI/MBG; Take Drug Again Assessment; PVAQ; and pupillometry.

The following secondary PD endpoints were calculated for each parameter of interest, as appropriate:

• Maximum (peak) effect (Emax);

• Time of maximum (peak) effect (TEmax);

• Minimum (peak) effect (Emin) for bipolar scales only;

• Time of minimum (peak) effect (TEmin) for bipolar scales only;

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• Area under the effect curve to 1 hour (AUE0-1h);

• Area under the effect curve to 2 hours (AUE0-2h);

• Area under the effect curve to 4 hours (AUE0-4h);

• Area under the effect curve to 8 hours (AUE0-8h);

• Area under the effect curve to 24 hours (AUE0-24h); and

• For Overall (Global) Drug Liking and the Take Drug Again Assessment, the Emax and mean response (Emean) averaging the 8 and 24 hour assessments.

Pharmacodynamic endpoints were estimated by standard non-compartmental methods for each subject in each Treatment Period of the Double-blind Treatment Phase. Calculation of Emax, Emin, and Emean used values through 24 hours post-dose; Drug Liking Emax was also derived from 0 to 8 hours post-dose (primary endpoint).

The following list provides the PD endpoint(s) that were evaluated for each PD parameter of interest:

• Drug Liking – All PD endpoints;

• Overall (Global) Drug Liking – Emean and Emax only for the Double-blind Treatment Period;

• Take Drug Again Assessment – Emean and Emax only for the Double-blind Treatment

Period; 8.0 and 24.0 hours post-dose;

• DEQ (any drug effects, high, good effects, bad effects, sick, nausea, sleepy, and dizzy) – All PD endpoints, except Emin and TEmin;

• PVAQ – Value collected at 24 hours post-dose;

• ARCI/MBG – All PD endpoints, except Emin and TEmin; and

• Pupillometry – All PD endpoints, except Emin, TEmin, and AUE0-24h.

2.1.3 Number of subjects (Planned and Analyzed):

Planned: Forty-eight completed subjects were planned for this study. A sample size of 48 completed subjects was estimated to provide at least 90% power to detect treatment differences of ≥ 9.0 points in maximum effect (Emax) for the bipolar Drug Liking visual analog scale (VAS), at the 1-sided significance level of 0.025, and estimated $\delta_1 = 3.5$, using a paired means test and correlation of 0.5, and assuming standard deviation differences of 11.0 points.

Analyzed: A total of 174 subjects entered the Drug Discrimination Phase, passed the Naloxone Challenge Test, and received at least one study drug dose in the Drug Discrimination Test; these subjects comprised the Drug Discrimination Safety Population. A total of 75 subjects passed the Drug Discrimination Test and entered the Double-blind Treatment Phase. The 75 subjects who entered the Double-blind Treatment Phase represent the Safety Population, of which 71 subjects

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had sufficient PK data and represent the PK Population. A total of 52 subjects completed the study and comprise the PD Population.

2.1.4 Pharmacodynamic Statistical Methodology used in Sponsor's analyses

All PD endpoints were analyzed using a linear mixed model with fixed effects for sequence, period, and treatment, and a random effect for subject nested in sequence. Least-squares (LS) means along with 95% confidence intervals (CIs) were provided for each treatment. Least-squares mean differences along with 95% CIs were provided for all pairwise treatment comparisons between treatments. The distribution of the residuals from each parametric model was examined to determine whether substantial departures from normality were apparent using the Shapiro Wilk test (tested at $\alpha = 0.01$). If the residuals were not normally distributed, a non-parametric analysis (the same procedure after ranked transformation) was to be provided in addition to the parametric analysis.

The primary analysis was based on the pairwise comparison between chewed Oxycodone

DETERx and crushed IR oxycodone fasted for Drug Liking Emax with the following hypothesis:

$$H_0: \mu_C - \mu_T \leq (\mu_C - 50)\,\delta^* \text{ versus } H_a: \mu_C - \mu_T > (\mu_C - 50)\,\delta^*$$

where $0.1 < \delta^* < 1$, $(\mu_C - 50)\,\delta^*$ was defined as δ_1. μ_C is the mean of the control treatment, crushed IR oxycodone 40 mg in solution fasted (Treatment E), and μ_T is the mean of the test treatment, chewed Oxycodone DETERx fasted (Treatment D) or chewed Oxycodone DETERx HFHC (Treatment C). A δ^* of 0.1 was used in the primary statistical analysis and if the test results were statistically significant, then the δ^* value was incremented by 0.05 until a statistically nonsignificant result was obtained for the primary statistical analyses. The last δ^* prior to non-significance was identified and footnoted in the summary table of the analyses for the DEQ Drug Liking outcome measure.

Additionally, the hypothesis for the validation test for Drug Liking Emax between IR oxycodone and placebo treatment was:

$$H_0: \mu_C - \mu_P \leq \delta_2 \text{ versus } H_a: \mu_C - \mu_P > \delta_2$$

where $\delta_2 = 15$.

For PD statistical analyses, significance for the primary comparisons was declared if the lower 95% CI was greater than δ1. Significance for the validation test was declared if the lower 95% confidence interval was greater than δ2. Significance testing for all other endpoints and comparisons was 2-tailed using $\alpha = 0.05$, unless otherwise specified.

The following treatment comparisons were made for each of the PD endpoints:

- Treatment E (crushed IR oxycodone fasted) versus Treatment F (placebo HFHC; Validity);

- Treatment E (crushed IR oxycodone fasted) versus Treatment D (chewed Oxycodone DETERx fasted; Primary Comparison);

- Treatment E (crushed IR oxycodone fasted) versus Treatment C (chewed Oxycodone DETERx HFHC; Primary comparison);

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• Treatment C (chewed Oxycodone DETERx HFHC) versus Treatment A (intact Oxycodone DETERx HFHC; Secondary comparison);

• Treatment D (chewed Oxycodone DETERx fasted) versus Treatment A (intact Oxycodone DETERx HFHC; Secondary comparison);

• Treatment D (chewed Oxycodone DETERx fasted) versus Treatment B (intact Oxycodone DETERx fasted; Secondary comparison);

• Treatment E (crushed IR oxycodone fasted) versus Treatment A (intact Oxycodone DETERx HFHC);

• Treatment E (crushed IR oxycodone fasted) versus Treatment B (intact Oxycodone DETERx fasted);

• Treatment A (intact Oxycodone DETERx HFHC) versus Treatment F (placebo HFHC);

• Treatment B (intact Oxycodone DETERx fasted) versus Treatment F (placebo HFHC);

• Treatment C (chewed Oxycodone DETERx HFHC) versus Treatment F (placebo HFHC);

• Treatment D (chewed Oxycodone DETERx fasted) versus Treatment F (placebo HFHC).

Percent Reduction and Responder Analysis of Percent Reduction

Percent Reduction

For the parameter of Emax based on Drug Liking, percent reductions were calculated for each subject for both test treatments as:

$$\%reduction = \begin{cases} \frac{c_i - t_i}{c_i - 50} \times \left(1 - \frac{p_i - 50}{50}\right) \times 100\%, \ i = 1,2,...n, \ if \ p_i > 55; \\ \frac{c_i - t_i}{c_i - 50} \times 100\%, \quad i = 1,2,...n, \qquad if \ p_i \le 55. \end{cases}$$

where ci, ti, and pi are the Drug Liking Emax values for the control, crushed IR oxycodone fasted (Treatment E), test, chewed Oxycodone DETERx HFHC (Treatment C) or chewed Oxycodone DETERx fasted (Treatment D), and the placebo HFHC (Treatment F), respectively; from the ith subject; and n is the sample size. The % reduction was calculated if data for the active control, test product, and placebo were available. In cases where 1 of those values was not available percent reduction was set to missing. In cases where the control was equal to 50, the percent reduction was set to the largest negative percent observed in the study for that comparison; if no negative percent existed (or it was less than -101%) then the percent reduction was set to -101%. The number and percent of subjects with % reductions falling within 10% increments are presented (i.e., 0% to 10% reduction, 10% to 20% reduction, etc.) for % reduction for Treatment C and % reduction for Treatment D.

Responder Analysis

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The % reduction in Drug Liking Emax was used to analyze the data using a responder analysis for Treatments D, C, B, and A. A responder was defined as a subject who had at least a pre-specified level of reduction, where levels from 0 to 100% in 10% increments are presented in a sensitivity analysis. The number and percent of subjects determined as responders and non-responders are presented. The binominal test of proportions was utilized to test the null hypothesis that 50% or fewer subjects were responders.

2.1.5 Sponsor's Pharmacodynamic Conclusions

Study validity was demonstrated by the statistically significant difference between crushed IR oxycodone fasted and placebo HFHC on the primary endpoint of Drug Liking Emax. The LS mean (95% CI) difference of 30.74 (26.38, 35.10) was statistically significant ($p < 0.0001$), and validity was confirmed since the lower bound of the 95% CI was higher than 15 points (i.e., $\delta 2$). In addition, crushed IR oxycodone fasted showed large and statistically significant differences compared with placebo HFHC on all secondary measures, including balance of effects (Overall [Global] Drug Liking, Take Drug Again, PVAQ), positive effects (Good Effects, High, ARCI/MBG), pharmacological effects (Any Effects, Sleepy, Dizzy), and pupillometry endpoints.

The primary comparisons of interest were between crushed IR oxycodone fasted and chewed Oxycodone DETERx under fasted or fed (HFHC) conditions. Drug Liking Emax of chewed Oxycodone DETERx fasted (LS mean ± [95% CI]: 73.71 ± 1.947 [69.87, 77.54]) was lower relative to crushed IR oxycodone fasted (86.76 ± 1.947 [82.93, 90.60]). The primary endpoint was met for this comparison, since the lower bound of the 95% CI of the LS mean difference was greater than 7.4 points (1-sided, $\alpha = 0.025$, $p = 0.0025$; i.e., by > 20%, based on the last tested δ^* of 0.20 prior to reaching statistical non-significance). Similarly, the LS mean ± SEM (95% CI) for chewed Oxycodone DETERx HFHC was 75.69 ± 1.947 (71.85, 79.52), which was statistically significantly lower compared with crushed IR oxycodone fasted. The lower bound of the 95% CI of the LS mean difference was greater than 5.5 points (1-sided, $\alpha = 0.025$, $p = 0.0038$), i.e., by > 15%, based on the last tested δ^* of 0.15 prior to reaching statistical non-significance.

The responder analysis showed that approximately 77% and 75% of subjects had some reduction in Drug Liking Emax with chewed Oxycodone DETERx fasted and chewed Oxycodone DETERx HFHC, respectively, relative to crushed IR oxycodone fasted, with the majority of subjects (65.4% and 61.5%) showing at least a 10% reduction in Drug Liking Emax following administration of chewed Oxycodone DETERx fasted and chewed Oxycodone DETERx HFHC, respectively, compared with crushed IR oxycodone fasted ($p < 0.05$).

Chewed Oxycodone DETERx treatments were also associated with statistically significantly lower Emax and AUE values than for crushed IR oxycodone fasted on most measures of balance of effects, including the key secondary endpoint of Take Drug Again Emax (median difference ± SEM [95% CI] = 9.00 ± 3.827 [1.00, 16.00], $p < 0.001$ for fasted, and 10.00 ± 4.082 [1.00, 17.00], $p < 0.001$ for HFHC), positive effects (High, Good Effects), pharmacological effects (Any Effects, Sleepy), and pupillometry. In addition to lower effects, Emax was statistically significantly delayed for chewed Oxycodone DETERx treatments compared with crushed IR oxycodone fasted on several of the measures, including Good Effects, High, Any Effects, and pupillometry. For both chewed Oxycodone DETERx fasted and HFHC treatments, the differences from crushed IR oxycodone fasted were less marked on the ARCI/MBG, Sleepy and Dizzy endpoints, though directionally supportive.

Additional secondary comparisons included those among the Oxycodone DETERx treatments (i.e., chewed versus intact). There were no statistical differences between chewed and intact treatments on the primary endpoint of Drug Liking Emax, Emax/Emean for Take Drug Again and Overall (Global) Drug Liking, and Emax on all other measures, indicating that chewing Oxycodone DETERx did not statistically significantly impact peak effects under fasted or HFHC conditions. There were statistically significant differences in early partial AUEs (up to 4 hours post-dose) on several of the measures, indicating that chewed Oxycodone DETERx was associated with greater effects earlier in the timecourse; however, few statistical differences were seen when considering effects up to 8 or 24 hours post-dose. The differences in early partial AUEs were generally supported by earlier TEmax for chewed Oxycodone DETERx fasted compared with the intact treatments; however, TEmax was not generally different for chewed versus intact Oxycodone DETERx HFHC.

All Oxycodone DETERx treatments were associated with statistically significantly greater effects compared with placebo on the majority of endpoints; however, consistent with the findings with chewed Oxycodone DETERx treatments, administration of intact Oxycodone DETERx under fasted or HFHC conditions was associated with statistically significantly lower and delayed effects relative to crushed IR oxycodone fasted on the primary endpoint of Drug Liking Emax and the majority of secondary endpoints.

Overall, the PD results indicate that chewed Oxycodone DETERx under fasted and fed (HFHC) conditions was statistically significantly less liked, associated with statistically significantly lower positive effects, and subjects were less willing to take these again compared with crushed IR oxycodone fasted. The outcomes of the planned sensitivity analyses for Drug Liking and Take Drug Again endpoints, which 1) excluded subjects with major protocol deviations (i.e., exclusion of Treatment Period 6 data for Subjects S268 and S271 due to incorrect meal assignment) and 2) considered the full 24-hour assessment interval (Drug Liking Emax and TEmax only), were consistent with the primary analyses. These results support that, when chewed, Oxycodone DETERx has statistically significantly lower abuse potential via the oral route compared with IR oxycodone. Furthermore, the abuse potential of Oxycodone DETERx was not meaningfully changed following manipulation via chewing as compared with the intact formulation.

2.2 Data Location

The analysis datasets are located at

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2.3 Reviewer's Assessment

All analyses were conducted from the stand point of the pharmacodynamics analysis.

2.3.1 Descriptive Statistics

The descriptive statistics of E_{max} and TE_{max} for the primary PD endpoint Drug Liking, and secondary PD endpoints, Drug Liking AUE [0-1h], Drug Liking AUE [0-2h], High, Overall Drug Liking and Take Drug Again are provided in Table 1 and Table 2. E_{max} is calculated as the maximum effect in the first 24 hours in the review's analysis. Table 1 summarizes the mean, standard deviation, minimum, the first quartile (Q1), median, the third quartile (Q3), and maximum of E_{max} for the six treatments in the study. Similarly table 2 summarizes results for TE_{max}.

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Table 1. E_{max} Descriptive Statistics for Drug Liking, Drug Liking AUE [0-1h], Drug Liking AUE [0-2h], High, Overall Drug Liking and Take Drug Again, PD population (N=52)

Parameter	Treatment	Mean	Std Dev	Min	Q1	Median	Q3	Max
Drug Liking	A: INTACT OXYCODONE DETERX HFHC	76.04	17.19	50.00	60.50	79.50	91.50	100.00
	B: INTACT OXYCODONE DETERX FASTED	74.06	15.05	50.00	64.00	73.50	82.50	100.00
	C: CHEWED OXYCODONE DETERX HFHC	75.56	14.65	50.00	63.50	75.50	87.00	100.00
	D: CHEWED OXYCODONE DETERX FASTED	73.35	14.93	50.00	63.50	73.50	82.50	100.00
	E: CRUSHED IR OXYCODONE IN SOLUTION FASTED	86.40	12.00	52.00	77.50	88.50	97.00	100.00
	F: PLACEBO HFHC	55.83	9.93	50.00	50.00	50.00	59.00	86.00
Drug Liking AUE [0-1h]	A: INTACT OXYCODONE DETERX HFHC	2.87	7.70	-5.35	0.00	0.00	2.04	38.26
	B: INTACT OXYCODONE DETERX FASTED	3.18	6.94	-0.63	0.00	0.38	3.93	43.90
	C: CHEWED OXYCODONE DETERX HFHC	2.45	3.82	0.00	0.00	0.69	4.00	18.69
	D: CHEWED OXYCODONE DETERX FASTED	4.62	5.35	0.00	0.19	2.51	7.98	22.64
	E: CRUSHED IR OXYCODONE IN SOLUTION FASTED	17.87	9.25	0.00	11.98	17.01	24.21	43.32
	F: PLACEBO HFHC	2.04	3.99	-0.38	0.00	0.00	2.26	17.30
Drug Liking AUE [0-2h]	A: INTACT OXYCODONE DETERX HFHC	8.87	16.74	-0.88	0.00	2.37	9.70	86.03
	B: INTACT OXYCODONE DETERX FASTED	14.68	16.87	0.00	2.00	9.61	22.63	93.74
	C: CHEWED OXYCODONE DETERX HFHC	10.57	13.22	-25.02	0.25	5.93	19.44	47.43
	D: CHEWED OXYCODONE DETERX FASTED	20.06	15.57	0.00	6.59	18.28	31.91	60.43
	E: CRUSHED IR OXYCODONE IN SOLUTION FASTED	47.35	20.30	0.00	32.52	50.87	62.71	91.58
	F: PLACEBO HFHC	4.96	9.05	-1.00	0.00	0.00	6.50	39.88
High	A: INTACT OXYCODONE DETERX HFHC	44.44	33.03	0.00	11.50	43.00	78.00	100.00
	B: INTACT OXYCODONE DETERX FASTED	42.69	30.15	1.00	16.00	39.00	69.00	100.00
	C: CHEWED OXYCODONE DETERX HFHC	44.44	30.71	0.00	19.00	37.50	72.50	97.00
	D: CHEWED OXYCODONE DETERX FASTED	43.79	30.85	0.00	17.00	47.50	72.50	93.00
	E: CRUSHED IR OXYCODONE IN SOLUTION FASTED	73.87	26.08	3.00	64.50	81.00	93.50	100.00
	F: PLACEBO HFHC	9.65	18.05	0.00	0.00	0.00	14.50	76.00
Overall Drug Liking	A: INTACT OXYCODONE DETERX HFHC	77.46	17.51	50.00	64.50	78.50	94.00	100.00
	B: INTACT OXYCODONE DETERX FASTED	76.73	17.33	47.00	63.50	77.50	92.00	100.00
	C: CHEWED OXYCODONE DETERX HFHC	76.25	17.95	38.00	60.00	77.00	92.50	100.00
	D: CHEWED OXYCODONE DETERX FASTED	75.73	17.83	50.00	58.50	76.50	91.50	100.00
	E: CRUSHED IR OXYCODONE IN SOLUTION FASTED	86.52	12.41	50.00	80.00	87.00	100.00	100.00

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	F: PLACEBO HFHC	55.46	13.05	50.00	50.00	50.00	51.00	100.00
Take Drug Again	A: INTACT OXYCODONE DETERX HFHC	78.17	21.18	0.00	61.50	81.00	100.00	100.00
	B: INTACT OXYCODONE DETERX FASTED	77.98	21.07	1.00	64.50	80.50	100.00	100.00
	C: CHEWED OXYCODONE DETERX HFHC	77.81	17.69	23.00	68.00	78.00	96.00	100.00
	D: CHEWED OXYCODONE DETERX FASTED	77.85	18.30	50.00	62.00	81.50	96.50	100.00
	E: CRUSHED IR OXYCODONE IN SOLUTION FASTED	87.69	12.90	50.00	81.00	90.50	100.00	100.00
	F: PLACEBO HFHC	50.79	21.41	0.00	50.00	50.00	50.50	100.00

The Emax descriptive statistics for Drug Liking VAS, as can be seen in table 1, for placebo, the mean was 55.8, slightly above neutral. The mean Emax score (86.4) for crushed IR oxycodone was highest, followed by Emax scores for the intact and chewed DETERx treatments (fasted and HFHC), which were at least 10 points lower. Median scores were generally similar to the mean scores.

For Drug Liking AUE [0-1h] and Drug Liking AUE [0-2h], crushed IR oxycodone had the highest mean and median among the six treatments.

For High VAS, the mean Emax scores were <10 for the placebo. The mean Emax scores for the intact and chewed DETERx treatments (fasted and HFHC) were almost 30 points lower comparing with crushed IR oxycodone (73.9).

For Overall Drug Liking VAS, mean Emax was lowest for placebo (55.5), followed by intact and chewed DETERx treatments (fasted and HFHC), while crushed IR oxycodone had the highest mean Emax score (86.5).

For Take Drug Again VAS, mean Emax was lowest for placebo (50.8), followed by intact and chewed DETERx treatments (fasted and HFHC), while crushed IR oxycodone had the highest mean Emax score (87.7).

Table 2. TE_{max} Descriptive Statistics for Drug Liking and High, PD population (N=52)

Parameter	Treatment	Mean	Std Dev	Min	Q1	Median	Q3	Max
Drug Liking	A: INTACT OXYCODONE DETERX HFHC	4.82	3.49	0.25	1.75	4.00	6.00	12.00
	B: INTACT OXYCODONE DETERX FASTED	3.75	2.65	0.25	2.00	3.00	5.00	12.00
	C: CHEWED OXYCODONE DETERX HFHC	4.67	2.83	0.25	3.00	4.00	6.00	12.00
	D: CHEWED OXYCODONE DETERX FASTED	2.38	1.77	0.25	1.00	2.00	3.00	8.00
	E: CRUSHED IR OXYCODONE IN SOLUTION FASTED	1.92	2.24	0.25	0.75	1.00	2.00	12.00
	F: PLACEBO HFHC	1.73	4.80	0.25	0.25	0.25	1.00	24.00
High	A: INTACT OXYCODONE DETERX HFHC	4.38	2.86	0.25	1.75	5.00	6.00	12.00
	B: INTACT OXYCODONE DETERX FASTED	3.61	2.14	0.25	2.00	3.00	4.50	8.00

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	C: CHEWED OXYCODONE DETERX HFHC	4.40	2.23	0.25	3.00	4.00	6.00	8.00
	D: CHEWED OXYCODONE DETERX FASTED	2.91	2.36	0.25	1.50	2.00	4.00	12.00
	E: CRUSHED IR OXYCODONE IN SOLUTION FASTED	1.60	1.29	0.50	1.00	1.00	2.00	8.00
	F: PLACEBO HFHC	0.77	0.98	0.25	0.25	0.25	1.00	4.00

TEmax is a secondary PD parameter, the larger the TEmax value, the longer for a subject to reach the Emax. So longer time to reach peak TEmax indicates the treatment has potential abuse-deterrence.

From table 2, for Drug Liking VAS of the active treatments, TEmax was earliest for crushed IR oxycodone fasted (mean=1.92 hour, median=1.0 hour), followed by chewed Oxycodone DETERx fasted treatment (mean=2.38 hour, median=2.0 hour), and latest for chewed Oxycodone DETERx HFHC treatment (mean=4.67 hour, median=4.0 hour). Similarly for High VAS, chewed Oxycodone DETERx HFHC treatment had TEmax (mean=4.4 hour, median=4.0 hour) longer than the TEmax of chewed Oxycodone DETERx fasted treatment (mean=2.91 hour, median=2.0 hour) and for crushed IR oxycodone fasted (mean=1.60 hour, median=1.0 hour).

Figure 1 shows the mean drug liking VAS over time, mean scores for crushed IR oxycodone rose rapidly to a peak (~81) at 1 hour post-dose and declined to neutral levels (50) by 24 hours post-dose. Mean peak Drug Liking scores were lower following administration of intact Oxycodone DETERx HFHC (~69) or fasted (~67), and following administration of chewed Oxycodone DETERx HFHC or fasted (~68). Furthermore, peak scores were delayed compared with crushed IR oxycodone (1 hour post-dose) to 2-3 hours post-dose following fasted DETERx treatments and 6 hours post-dose following HFHC treatments. Mean scores for all Oxycodone DETERx treatments returned to neutral levels (50) by 24 hours post-dose. Mean placebo scores remained close to neutral (50) throughout the time course.

Figure 1. Mean Drug Liking VAS Scores over time (PD Population, N=52)

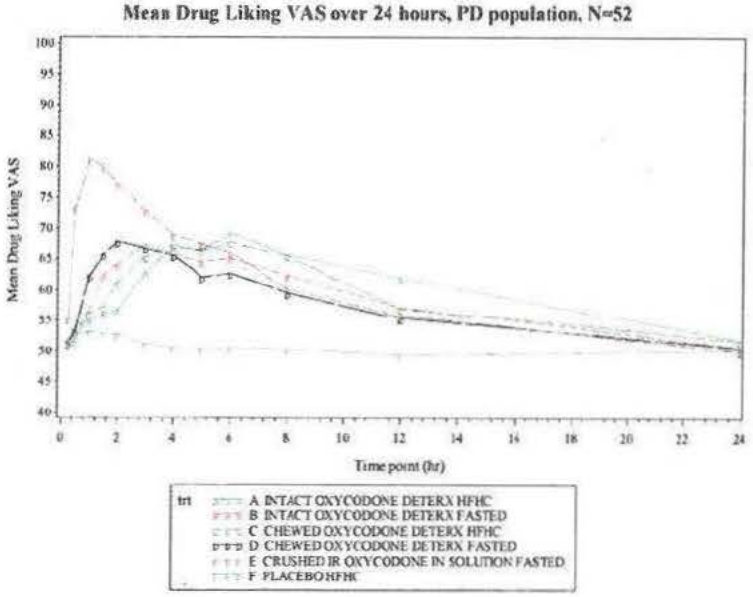
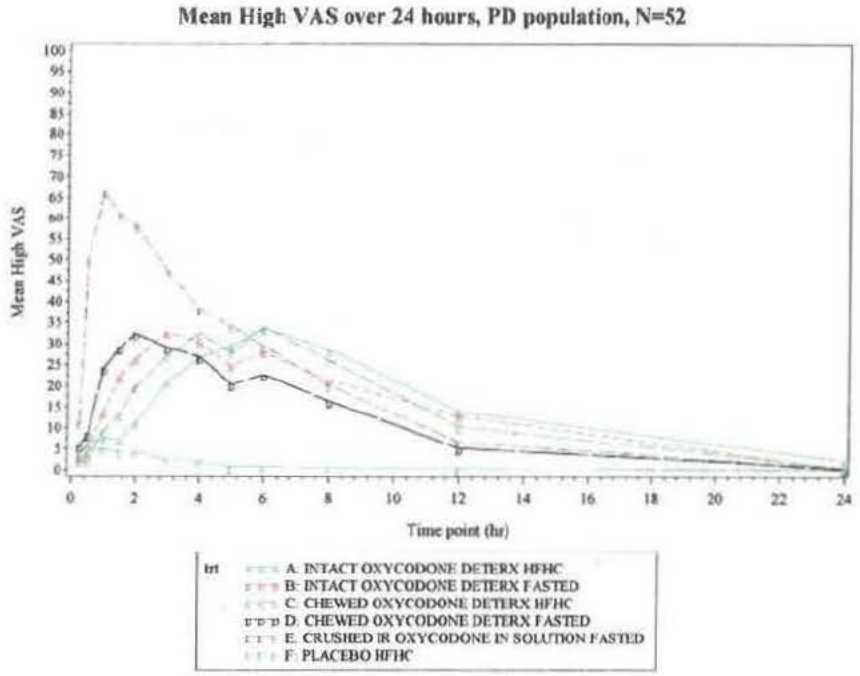


Figure 2 presented the Mean High VAS scores over time. Mean scores for crushed IR oxycodone fasted rose rapidly to a peak (~66) at 1 hour post-dose and declined to neutral (0) by 24 hours post-dose. Mean peak High scores were lower following administration of intact Oxycodone DETERx HFHC (~33.5) or fasted (~32.5), and following administration of chewed Oxycodone DETERx HFHC (~34) or fasted (~32). Furthermore, peak scores were delayed compared with crushed IR oxycodone to 2-3 hours following fasted DETERx treatments and 6 hours following HFHC treatments. Mean scores for all Oxycodone DETERx treatments returned to neutral levels (< 5) by 24 hours post-dose. Mean placebo scores remained close to neutral throughout the time course.

Figure 2. Mean High VAS Scores over time (PD Population, N=52)



Individual E_{max} scores are displayed by subject for all treatments from Figure 3 to Figure 6, each row represent one patient with six treatments, the darker color means the more like. We can compare the E_{max} score for each patient at different treatment. The heatmaps show general more like for crushed IR oxycodone fasted comparing with chewed Oxycodone DETERx HFHC and chewed Oxycodone DETERx fasted, some subjects had high placebo response, there were 12 out of 52 (23%) subjects had placebo response >60.

Figure 3. Heatmap for Emax of Drug Liking VAS by treatment

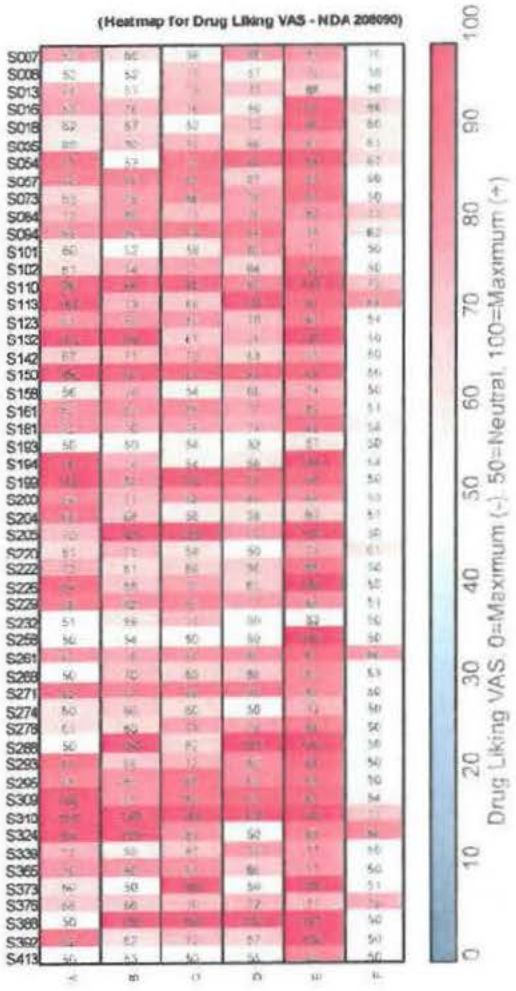


Figure 4. Heatmap for Emax of High VAS by treatment

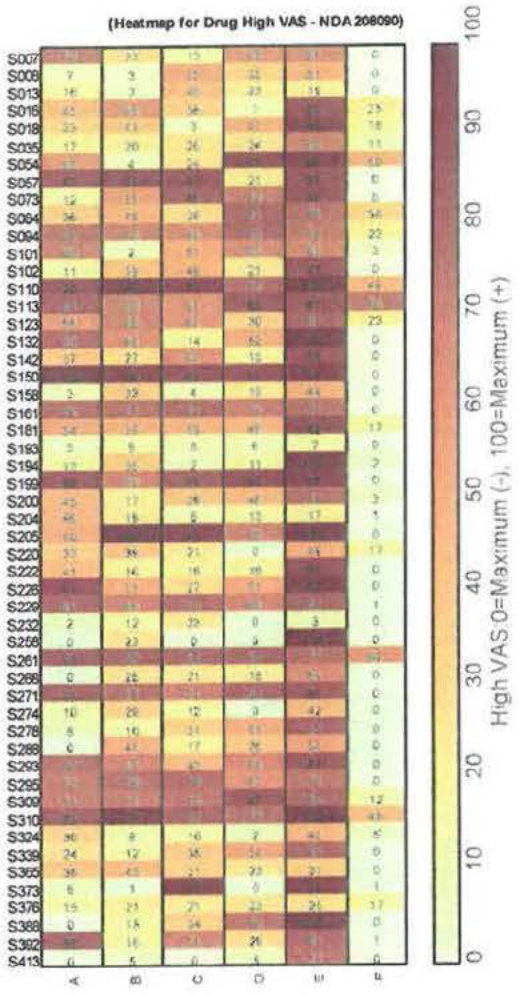


Figure 5. Heatmap for Emax of Overall Drug Liking VAS by treatment

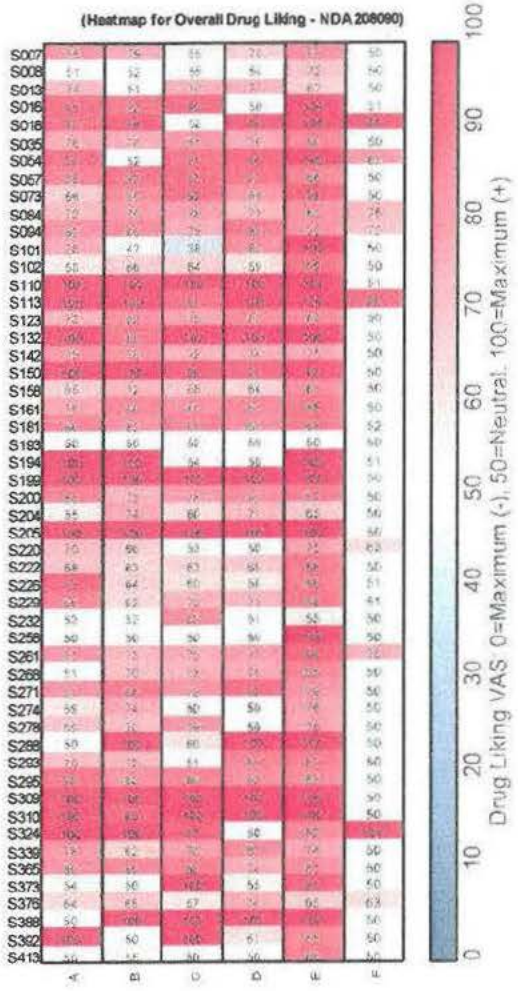
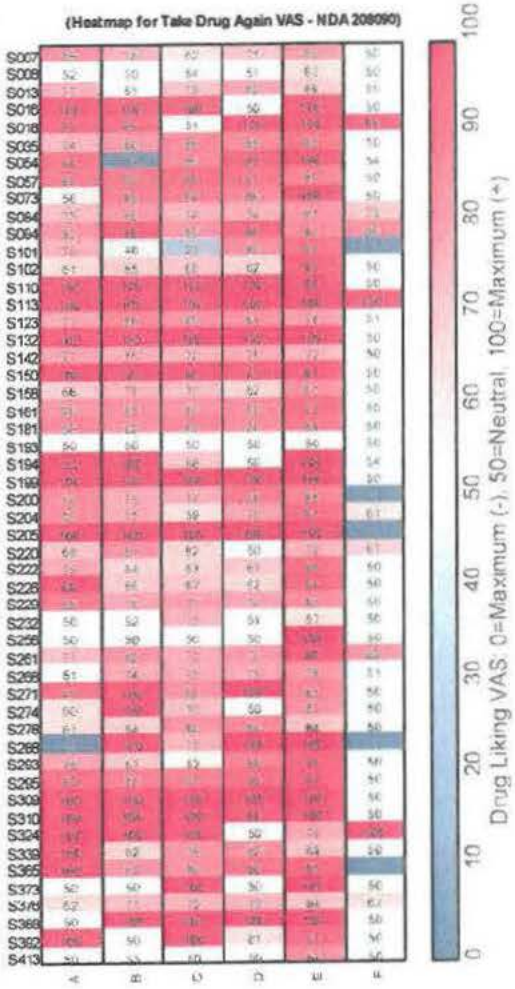


Figure 6. Heatmap for Emax of Take Drug Again VAS by treatment



2.3.2 Statistical Analysis

Validation of the Appropriateness of the Positive Control

The hypothesis for the validation test for Drug Liking Emax between IR oxycodone and placebo treatment was:

$$H_0: \mu_C - \mu_P \leq \delta_2 \text{ versus } H_a: \mu_C - \mu_P > \delta_2$$

where $\delta_2 = 15$.

The comparison of crushed IR oxycodone fasted to placebo HFHC was made to confirm study validity. Table 3 showed least squares mean Emax for Drug Liking was higher for crushed IR oxycodone fasted than placebo HFHC (86.76) versus 56.13. The LS mean (95% CI) difference of

30.67 (26.29, 35.05) was statistically significant ($p < 0.0001$), and validity was confirmed since the lower bound of the 95% CI was higher than 15 points (i.e., δ_2).

Table 3 . Validation test for Drug Liking Emax of the Positive Control, PD Population.

Treatments	LS Mean	StdE	Lower	Upper	
E: CRUSHED IR OXYCODONE FASTED	86.80	1.93	83.00	90.60	
F: PLACEBO HFHC	56.13	1.93	52.33	59.94	
Contrasts (difference)	LS Mean	StdE	Pr > |t|	Lower	Upper
CRUSHED IR OXYCODONE FASTED vs. PLACEBO HFHC (E-F)- **Validation Test**	30.67	2.22	<.0001	26.29	35.05

Analysis of Primary Endpoints for Primary Comparisons

PD parameters of interest for the Treatment Phase will be analyzed using a mixed-effect model if the data is normally distributed. Parameters that don't meet these criteria will be analyzed non-parametrically.

In this study, for Drug Liking, Drug Liking AUE [0-1h], Drug Liking AUE [0-2h], High and Overall Drug Liking, the normality assumption tests were met, the reviewer analyzed the hypotheses of the primary objective using the mixed-effect model, with period, sequence and treatment as fixed effects, and subject nested within treatment sequence as random effect. For Take Drug Again, the normality assumption test was not met, so non-parametric method was conducted. TEmax of Drug liking VAS and High VAS were also conducted by non-parametric method. Table 3 to table 8 are the statistical analysis results for Emax of Drug Liking, Drug Liking AUE [0-1h], Drug Liking AUE [0-2h], High, Overall Drug Liking and Take Drug Again respectively. Table 9 is the statistical analysis results for TEmax of Drug Liking and High.

Table 4. Statistical Analysis of the mean difference in Emax for Drug Liking VAS, PD Population.

Treatments	LS Mean	StdE	Lower	Upper	
A: INTACT OXYCODONE DETERX HFHC	76.50	1.93	72.70	80.30	
B: INTACT OXYCODONE DETERX FASTED	74.57	1.93	70.77	78.37	
C: CHEWED OXYCODONE DETERX HFHC	75.87	1.93	72.07	79.67	
D: CHEWED OXYCODONE DETERX FASTED	73.71	1.93	69.91	77.51	
E: CRUSHED IR OXYCODONE FASTED	86.80	1.93	83.00	90.60	
F: PLACEBO HFHC	56.14	1.93	52.34	59.94	
Contrasts (difference)	LS Mean	StdE	Pr > |t|	Lower	Upper
E v F (Validation)	30.67	2.22	<.0001	26.29	35.05
E v D (Primary)	13.10	2.22	<.0001	8.72	17.48
E v C (Primary)	10.93	2.23	<.0001	6.54	15.32

Table 4 presents results of the inferential analysis of Drug Liking Emax for the chewed Oxycodone DETERx fasted and HFHC treatments versus crushed IR oxycodone fasted. The LS mean (95% CI) Emax for Drug Liking for chewed Oxycodone DETERx fasted and for chewed Oxycodone DETERx HFHC were 73.71 (69.91, 77.51) and 75.87 (72.07, 79.67), respectively,

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compared with 86.80 (83.00, 90.60) for crushed IR oxycodone fasted. The LS mean (95% CI) differences were 13.10 (8.72, 17.48) and 10.93 (6.54, 15.32), respectively, both comparisons showed that the differences were statistically significant (P<0.0001)

Table 5. Statistical Analysis of the mean difference in Emax for Drug Liking AUE [0-1h], PD Population.

Treatments	LS Mean	StdE	Lower	Upper
A: INTACT OXYCODONE DETERX HFHC	2.99	0.90	1.21	4.77
B: INTACT OXYCODONE DETERX FASTED	3.29	0.90	1.51	5.07
C: CHEWED OXYCODONE DETERX HFHC	2.56	0.90	0.78	4.34
D: CHEWED OXYCODONE DETERX FASTED	4.81	0.90	3.03	6.59
E: CRUSHED IR OXYCODONE FASTED	18.10	0.90	16.32	19.89
F: PLACEBO HFHC	2.19	0.90	0.41	3.97

Contrasts (difference)	LS Mean	StdE	Pr > |t|	Lower	Upper
E v F (Validation)	15.91	1.15	<.0001	13.64	18.18
E v D (Primary)	13.29	1.15	<.0001	11.02	15.56
E v C (Primary)	15.55	1.15	<.0001	13.27	17.82

Drug Liking results for AUE [0-1h] and AUE [0-2h] showed similar results as for Emax with significantly less liking for chewed Oxycodone DETERx fasted and HFHC than crushed IR oxycodone fasted ($p < 0.0001$).

Table 6. Statistical Analysis of the mean difference in Emax for Drug Liking AUE [0-2h], PD Population.

Treatments	LS Mean	StdE	Lower	Upper
A: INTACT OXYCODONE DETERX HFHC	9.26	2.15	5.03	13.50
B: INTACT OXYCODONE DETERX FASTED	15.11	2.15	10.87	19.35
C: CHEWED OXYCODONE DETERX HFHC	11.11	2.15	6.87	15.35
D: CHEWED OXYCODONE DETERX FASTED	20.71	2.15	16.47	24.95
E: CRUSHED IR OXYCODONE FASTED	47.89	2.15	43.65	52.13
F: PLACEBO HFHC	5.36	2.15	1.12	9.59

Contrasts (difference)	LS Mean	StdE	Pr > |t|	Lower	Upper
E v F (Validation)	42.54	2.83	<.0001	36.96	48.11
E v D (Primary)	27.18	2.83	<.0001	21.60	32.76
E v C (Primary)	36.79	2.84	<.0001	31.20	42.38

Table 7. Statistical Analysis of the mean difference in Emax for High VAS, PD Population.

Treatments	LS Mean	StdE	Lower	Upper
A: INTACT OXYCODONE DETERX HFHC	45.22	3.91	37.51	52.93
B: INTACT OXYCODONE DETERX FASTED	43.73	3.91	36.02	51.43
C: CHEWED OXYCODONE DETERX HFHC	45.26	3.91	37.55	52.97
D: CHEWED OXYCODONE DETERX FASTED	44.58	3.91	36.87	52.29
E: CRUSHED IR OXYCODONE FASTED	74.71	3.91	67.00	82.42
F: PLACEBO HFHC	10.28	3.91	2.57	17.99

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Contrasts (difference)	LS Mean	StdE	Pr > |t|	Lower	Upper
E v F (Validation)	64.4	4.1	<.0001	56.3	72.5
E v D (Primary)	30.1	4.1	<.0001	22.0	38.2
E v C (Primary)	29.4	4.1	<.0001	21.3	37.6

High Emax was statistically significantly higher for crushed IR oxycodone fasted compared with chewed Oxycodone DETERx fasted and HFHC ($p < 0.0001$).

Table 8. Statistical Analysis of the mean difference in Emax for Overall Drug Liking, PD Population.

Treatments	LS Mean	StdE	Lower	Upper
A: INTACT OXYCODONE DETERX HFHC	78.05	2.24	73.64	82.47
B: INTACT OXYCODONE DETERX FASTED	77.32	2.24	72.90	81.74
C: CHEWED OXYCODONE DETERX HFHC	76.61	2.24	72.19	81.02
D: CHEWED OXYCODONE DETERX FASTED	76.02	2.24	71.60	80.43
E: CRUSHED IR OXYCODONE FASTED	86.92	2.24	82.51	91.34
F: PLACEBO HFHC	55.94	2.24	51.53	60.36

Contrasts (difference)	LS Mean	StdE	Pr > |t|	Lower	Upper
E v F (Validation)	30.98	2.52	<.0001	26.02	35.94
E v D (Primary)	10.91	2.52	<.0001	5.95	15.87
E v C (Primary)	10.32	2.52	<.0001	5.34	15.29

Overall Drug Liking Emax was statistically significantly higher for crushed IR oxycodone fasted compared with chewed Oxycodone DETERx fasted and HFHC ($p < 0.0001$).

Table 9. Nonparametric Analyses of Take Drug Again Emax, PD Population

Treatment Difference	Median Difference	Interquartile Range	P-value
E v F (Validation)	39.5	31	<.0001
E v D (Primary)	4.50	19.5	<.0001
E v C (Primary)	3.50	18	<.0001

Take Drug Again Emax was statistically significantly higher for crushed IR oxycodone fasted compared with chewed Oxycodone DETERx fasted and HFHC ($p < 0.0001$).

Percent Reduction Analysis

Percent reduction analysis is an important abuse potential measure, and it is recommended for the clinical abuse potential studies. For the parameter of Drug Liking Emax VAS, percent reductions were calculated for each subject for both test treatments as:

$$\%reduction = \begin{cases} \frac{C-T}{C-50} \times \left(1 - \frac{P-50}{50}\right) \times 100\%, & if\ P > 55; \\ \frac{C-T}{C-50} \times 100\%, & if\ P \le 55. \end{cases}$$

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where C and T were the Emax values for the control and the test product, respectively, and P was the Emax value of placebo. The percent reduction was calculated if data for the active control and test product were available. In cases where one of those values was not available or the control was equal to 50, percent reduction was to be set to 0.

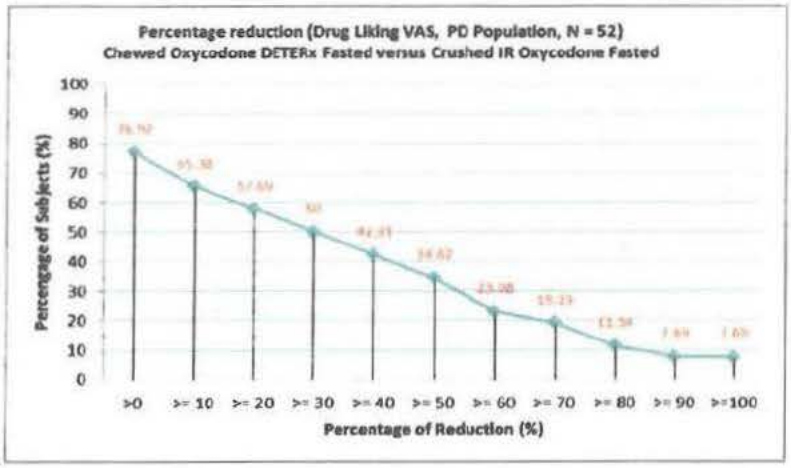
Crushed Roxicodone vs. Ground Oxycodone ARIR

From Table 10 and Figure 7, 40 out of the 52 subjects who completed the study (~77%) had some reduction in Drug Liking with Chewed Oxycodone DETERx Fasted (Treatment D) compare to Crushed IR Oxycodone Fasted (Treatment E), while 23% subjects had no reduction or negative reduction. 26 subjects (50%) experienced at least a 30% reduction and 18 subjects (~35%) had at least a 50% reduction in Emax of Drug Liking with Chewed Oxycodone DETERx Fasted (Treatment D) compare to Crushed IR Oxycodone Fasted (Treatment E).

Table 10. %reduction, Drug Liking VAS Emax, Chewed Oxycodone DETERx Fasted (Treatment D) versus Crushed IR Oxycodone Fasted (Treatment E) (PD Population, N=52)

Percentage of Reduction (%)	Frequency	Percentage of subjects (%)
>0	40	76.92
≥10	34	65.38
≥20	30	57.69
≥30	26	50
≥40	22	42.31
≥50	18	34.62
≥60	12	23.08
≥70	10	19.23
≥80	6	11.54
≥90	4	7.69
≥100	4	7.69

Figure 7. %reduction, Drug Liking VAS Emax, Chewed Oxycodone DETERx Fasted (Treatment D) versus Crushed IR Oxycodone Fasted (Treatment E) (PD Population, N=52)

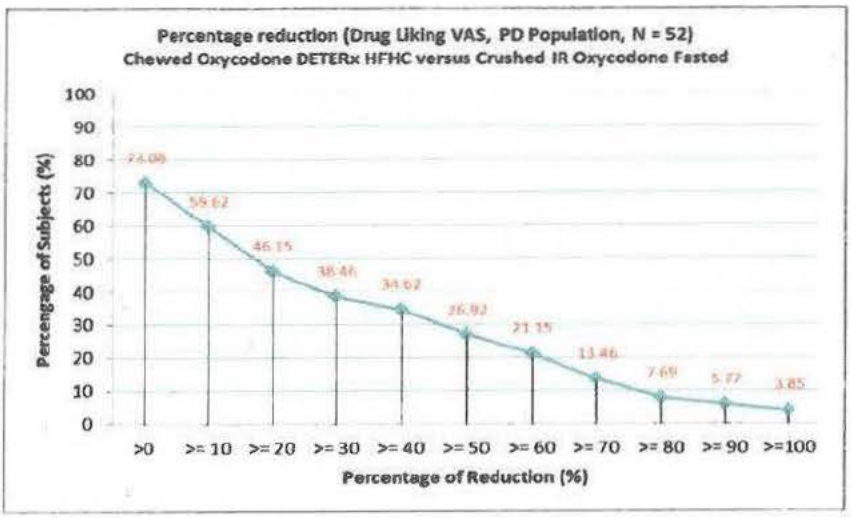


From Table 11 and Figure 8, 38 out of the 52 subjects who completed the study (~73%) had some reduction in Drug Liking with Chewed Oxycodone DETERx HFHC (Treatment C) versus Crushed IR Oxycodone Fasted (Treatment E), while 27% subjects had no reduction or negative reduction. 20 subjects (~38%) experienced at least a 30% reduction and 14 subjects (~27%) had at least a 50% reduction in Emax of Drug Liking with Chewed Oxycodone DETERx HFHC (Treatment C) versus Crushed IR Oxycodone Fasted (Treatment E).

Table 11. %reduction, Drug Liking VAS Emax, Chewed Oxycodone DETERx HFHC (Treatment C) versus Crushed IR Oxycodone Fasted (Treatment E) (PD Population, N=52)

Percentage of Reduction (%)	Frequency	Percentage of subjects (%)
>0	38	73.08
≥10	31	59.62
≥20	24	46.15
≥30	20	38.46
≥40	18	34.62
≥50	14	26.92
≥60	11	21.15
≥70	7	13.46
≥80	4	7.69
≥90	3	5.77
≥100	2	3.85

Figure 8. %reduction, Drug Liking VAS Emax, Chewed Oxycodone DETERx HFHC (Treatment C) versus Crushed IR Oxycodone Fasted (Treatment E) (PD Population, N=52)



2.3.3 Primary statistical analysis using 2015 new guidance method

The 2015 FDA Guidance for Industry: Abuse-Deterrent Opioids – Evaluation and Labeling suggests the primary analysis of abuse-deterrent effects should be based on the comparison of means between crushed, chewed, or otherwise modified T and C with an abuse deterrence margin on drug liking VAS. That is, test

$$H_0 : \mu_C - \mu_T \le \delta_1 \; vs \; H_a : \mu_C - \mu_T > \delta_1 \quad (1)$$

Where μ_C and μ_T denote means of positive control and test drug respectively, and $\delta_1 = \delta^*(\mu_C - 50), 0 < \delta^* < 1$, formula (1) is equivalent to:

$$H_0 : \mu_T - (1-\delta^*)\mu_C \ge 50\delta^* \; vs \; H_a : \mu_T - (1-\delta^*)\mu_C < 50\delta^* \quad (2)$$

Study validation is denoted as following, Where μ_P denotes mean of placebo and $\delta_2 \ge 15$.

$$H_0 : \mu_C - \mu_P \le \delta_2 \; vs \; H_a : \mu_C - \mu_T > \delta_2 \quad (3)$$

Both tests are one-sided at the 2.5% significance level.

These hypotheses can be extended to the other PD endpoints using unipolar scale such as High VAS with $\delta_1 = \delta^* \mu_C \; (0 < \delta^* < 1)$ and $\delta_2 \ge 30$.

The reviewer used δ^* =0.10 with 0.05 increment for each primary comparison, and stopped once an insignificant result was obtained. Since for Take Drug Again, the normality assumption test was not met, so non-parametric method was conducted as was shown earlier. The following table lists the test results by following 2015 FDA new guidance.

Table 12. Summary of primary analysis result for Drug Liking, High and Overall Drug Liking by following 2015 FDA new guidance.

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Parameter	Comparison	Test type	Estimate Diff	Std Err	Test value	P-value
Drug Liking	E v F (Validation)	Validation	30.67	2.22	15	<.0001
	E v D (Primary)	Primary (δ^*=0.20)	4.26	2.03	10	0.0025
	E v C (Primary)	Primary (δ^*=0.15)	2.09	2.08	7.5	0.0048
High	E v F (Validation)	Validation	64.44	4.11	30	<.0001
	E v D (Primary)	Primary (δ^*=0.30)	-7.72	3.63	0	0.0173
	E v C (Primary)	Primary (δ^*=0.25)	-10.77	3.70	0	0.002
Overall Drug Liking	E v F (Validation)	Validation	30.98	2.52	15	<.0001
	E v D (Primary)	Primary (δ^*=0.15)	2.13	2.35	7.5	0.0115
	E v C (Primary)	Primary (δ^*=0.10)	2.72	2.35	7.5	0.0216
		(δ^*=0.15)				

A: Intact Oxycodone DETERx HFHC, B: Intact Oxycodone DETERx Fasted, C: Chewed Oxycodone DETERx HFHC, D: Chewed Oxycodone DETERx Fasted, E: Crushed IR Oxycodone Fasted, F: Placebo HFHC

Table 12 shows that Emax of Crushed IR Oxycodone Fasted is significantly greater than Placebo HFHC (P<0.0001) for Drug Liking VAS, High VAS and Overall Drug Liking VAS, thereby confirming study validity.
For the primary comparison between E: Crushed IR Oxycodone Fasted vs. D: Chewed Oxycodone DETERx Fasted, D: Chewed Oxycodone DETERx Fasted had statistically significant 20% reduction in Emax of Drug Liking VAS, 30% reduction in Emax of High VAS, and 15% reduction in Emax of Overall Drug Liking VAS comparing with E: Crushed IR Oxycodone Fasted.

For the primary comparison between E: Crushed IR Oxycodone Fasted vs. C: Chewed Oxycodone DETERx HFHC, C: Chewed Oxycodone DETERx HFHC had statistically significant 15% reduction in Emax of Drug Liking VAS, 25% reduction in Emax of High VAS, and 15% reduction in Emax of Overall Drug Liking VAS comparing with E: Crushed IR Oxycodone Fasted.

3. Conclusions

The primary objective of this study was to evaluate the abuse liability and PK of oxycodone after intact and chewed oral administration of Oxycodone DETERx under fed (high-fat, high-calorie [HFHC]) and fasted conditions, and crushed IR oxycodone under fasted conditions.

The reviewer analyzed the primary PD endpoint Drug Liking, and the secondary PD endpoints: Drug Liking AUE [0-1h] Emax, Drug Liking AUE [0-2h] Emax, High, Take Drug Again and Overall Drug Liking. The results from the statistical reviewer's analyses establish that:

- The Crushed IR Oxycodone Fasted resulted in statistically significantly greater (p<0.0001) VAS scores compared to Placebo HFHC for Drug Liking, High and Overall Drug Liking, thereby validating these pharmacodynamic measures.

Reference ID: 4139182

- The LS mean (95% CI) Emax for Drug Liking for chewed Oxycodone DETERx fasted and for chewed Oxycodone DETERx HFHC were 73.71 (69.91, 77.51) and 75.87 (72.07, 79.67), respectively, compared with 86.80 (83.00, 90.60) for crushed IR oxycodone fasted. The LS mean (95% CI) differences were 13.10 (8.72, 17.48) and 10.93 (6.54, 15.32), respectively, both comparisons showed that the differences were statistically significant (P<0.0001).

- High Emax was statistically significantly higher for crushed IR oxycodone fasted compared with chewed Oxycodone DETERx fasted and HFHC ($p < 0.0001$).

- Overall Drug Liking Emax was statistically significantly higher for crushed IR oxycodone fasted compared with chewed Oxycodone DETERx fasted and HFHC ($p < 0.0001$.

- Take Drug Again Emax was statistically significantly higher for crushed IR oxycodone fasted compared with chewed Oxycodone DETERx fasted and HFHC ($p < 0.0001$).

- 40 out of the 52 subjects who completed the study (~77%) had some reduction in Drug Liking with Chewed Oxycodone DETERx Fasted (Treatment D) compare to Crushed IR Oxycodone Fasted (Treatment E). 26 subjects (50%) experienced at least a 30% reduction and 18 subjects (~35%) had at least a 50% reduction in Emax of Drug Liking with Chewed Oxycodone DETERx Fasted (Treatment D) compare to Crushed IR Oxycodone Fasted (Treatment E).

- 38 out of the 52 subjects who completed the study (~73%) had some reduction in Drug Liking with Chewed Oxycodone DETERx HFHC (Treatment C) versus Crushed IR Oxycodone Fasted (Treatment E). 20 subjects (~38%) experienced at least a 30% reduction and 14 subjects (~27%) had at least a 50% reduction in Emax of Drug Liking with Chewed Oxycodone DETERx HFHC (Treatment C) versus Crushed IR Oxycodone Fasted (Treatment E).

By following the 2015 new guidance:

- Emax of Crushed IR Oxycodone Fasted is significantly greater than Placebo HFHC (P<0.0001) for Drug Liking VAS, High VAS and Overall Drug Liking VAS, thereby confirming study validity.

- For the primary comparison between E: Crushed IR Oxycodone Fasted vs. D: Chewed Oxycodone DETERx Fasted, D: Chewed Oxycodone DETERx Fasted had statistically significant 20% reduction in Emax of Drug Liking VAS, 30% reduction in Emax of High VAS, and 15% reduction in Emax of Overall Drug Liking VAS comparing with E: Crushed IR Oxycodone Fasted.

- For the primary comparison between E: Crushed IR Oxycodone Fasted vs. C: Chewed Oxycodone DETERx HFHC, C: Chewed Oxycodone DETERx HFHC had statistically significant 15% reduction in Emax of Drug Liking VAS, 25% reduction in Emax of High VAS, and 15% reduction in Emax of Overall Drug Liking VAS comparing with E: Crushed IR Oxycodone Fasted.

Additional comments

1. On page 89 of the Clinical Study Report, Table 9 shows Inferential Analysis for Drug Liking Emax for Primary Comparison, in the footnote, sponsored mentioned 'T was statistically lower than C by > 7.4 or 5.5 points, respectively, using d* = 0.20 or 0.15, respectively, the last value prior to non-significance;'

   Reviewer's comments: For the hypothesis testing,

   $H_0 : \mu_C - \mu_T \le (\mu_C - 50)\delta^*$ *vs* $H_a : \mu_C - \mu_T > (\mu_C - 50)\delta^*$

   μ_C is unknown, you should not use the least square mean of control to replace μ_C. Instead, you may test following hypothesis which is equivalent to above but only need to specify δ^*:

   $H_0 : \mu_T - (1-\delta^*)\mu_C \ge 50\delta^*$ *vs* $H_a : \mu_T - (1-\delta^*)\mu_C < 50\delta^*$

2. As to the percent reduction profile plot, you should use >0 instead of ≥0 for the first data point.

4. References

1) Guidance for Industry: Assessment of Abuse Potential for Drugs (January 2017) http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm198650.pdf

2) Guidance for Industry: Abuse Deterrent Opioids—Evaluation and Labeling (April 2015) http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm334743.pdf

3) Chen, Klein and Calderon (2012) poster presentation at the 74th College on Problems of Drug Dependence (CPDD) annual scientific meeting held in Palm Springs.

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/s/

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08/17/2017

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 208090/S-004

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA or BLA Number	208090 S004
Link to EDR	\\CDSESUB1\evsprod\NDA208090\0071 \\CDSESUB1\evsprod\NDA208090\0098
Submission Date	10/4/2016 and major amendment submitted on 3/24/2017
Submission Type	*Standard review*
Brand Name	Xtampza
Generic Name	Oxycodone Extended Release Capsules
Dosage Form and Strength	Capsules with
Route of Administration	Oral
Proposed Indication	Pain Management
Applicant	Collegium Pharmaceuticals
Associated IND	*[IND 75786]*
OCP Review Team	*[Srikanth C. Nallani, Ph.D.]*
OCP Final Signatory	*[Yun Xu, Ph.D.]*

Reference ID: 4161285

Table of Contents

1. EXECUTIVE SUMMARY

1.1 Recommendations

The submission is acceptable from clinical pharmacology perspective.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

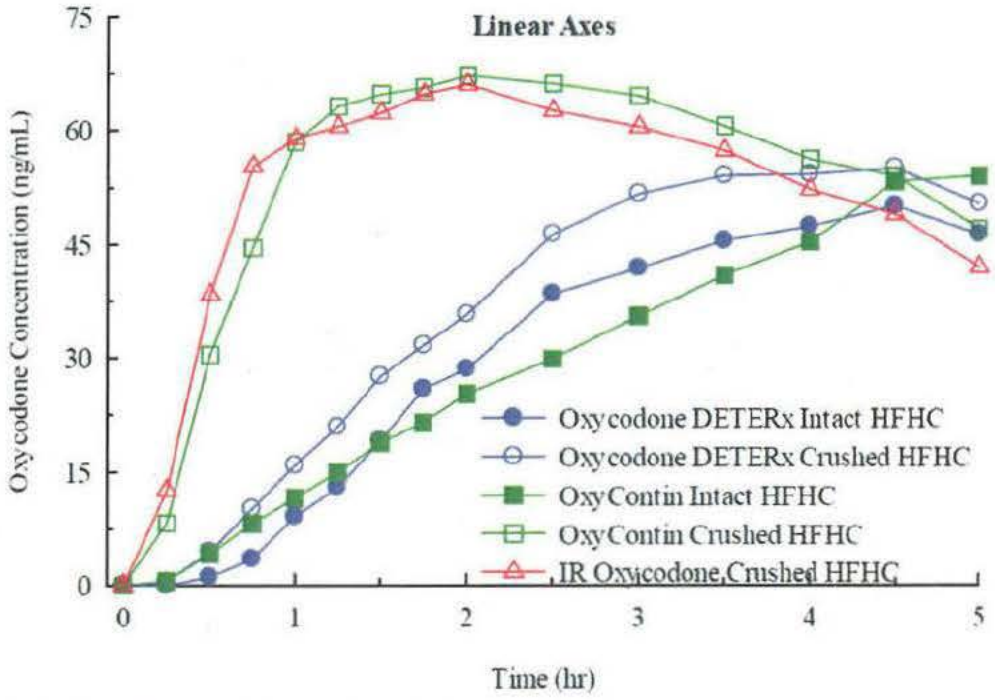
Xtampza was approved in 2016 with information in label section 9 related to intranasal abuse deterrence and limited oral abuse deterrence claims. In the current submission Collegium submitted study CP-OXYDET-29, a category 2 PK only oral abuse liability study comparing Xtampza and OxyContin fed (Oxycodone extended-release tablets) following chewing. The purpose of this study was to reevaluate the impact of tampering on the PK of the Oxycodone DETERx capsule compared with another abuse-deterrent formulation of oxycodone –OxyContin fed (Oxycodone extended-release tablets) – in healthy, naltrexone-blocked subjects using a tampering method known to result in particle size reduction in vitro. Previously, category 2 PK only oral abuse liability study CP-OXYDET-25 confirmed and extended the findings of product manipulation studies conducted using Xtampza by directly comparing the effect of crushing on the PK for Xtampza and OxyContin fed (Oxycodone extended-release tablets) when administered after a meal.

In March of 2017, while the NDA review was ongoing, Collegium submitted results of study CP-OXYDET-28, another Category 3 PK-PD abuse liability study. Study CP-OXYDET-28 was conducted to reevaluate the human abuse potential observations noted in Study CP-OXYDET-24 and used similar analyses for the oral route of administration. These studies compared intact and chewed Oxycodone DETERx (delivered in the fed and fasted states), IR oxycodone in solution (fasted), and placebo (fed). While there were similarities between the first oral human abuse potential study of Oxycodone DETERx (CPOXYDET-24), CP-OXYDET-28 was designed to address key considerations from the final FDA guidance, including enhanced subject selection in the Drug Discrimination Phase and improved training on PD assessments. Some of the differences between studies included, use of oxycodone 20 mg in the Drug Discrimination Phase in Study CP-OXYDET-24 compared to a higher dose of 40 mg used in both the Drug Discrimination Phase and the Treatment Phase of Study CP-OXYDET-28. In addition, the Drug Discrimination criteria were refined, including a higher minimum Drug Liking Emax response to oxycodone and narrower placebo response range, to ensure that an appropriately sensitive population was selected for enrollment into the Double-blind Treatment Phase.

PK results from Category 2 PK study CP-OXYDET-29:

In Category 2 PK study CP-OXYDET-29 healthy volunteers received different treatments with high-fat high-calorie meal under naltrexone block (n=37-39 completers). In this study, intact Xtampza was bioequivalent to intact OxyContin fed (Oxycodone extended-release tablets) in fed state. Highest plasma levels were noted with crushed immediate release oxycodone tablets (mean Cmax = 78 ng/mL) and crushed OxyContin fed (Oxycodone extended-release tablets) tablets (mean Cmax = 80 ng/mL) administered orally. It should be noted that OxyContin fed (Oxycodone extended-release tablets) does not have oral abuse deterrence claims in the product label. The median Tmax for intact Xtampza was 3.5 hours and for OxyContin fed (Oxycodone extended-release tablets) it was 4.5 hours. It is noteworthy to mention an observed Tlag with all treatments, taken with food, as shown in the table below. Crushing of Oxycodone DETERx or Xtampza resulted in mean C_{max} and AUC values that were bioequivalent and a median Tmax that was unchanged (3.5 hours) relative to intact dosing. The mean concentration versus time profile for oxycodone is displayed on a linear scale below following different treatments over the first five hours for emphasis.

Figure: Mean Oxycodone Profile over the First Five Hours from Study CP-OXYDET-29.



HFHC=high-fat, high-calorie; IR=immediate-release; PK=pharmacokinetic
Source: Appendix 16.6.1, Figure 2

Table: Descriptive Statistics of Oxycodone PK Parameters from Study CP-OXYDET-29.

Parameter*	Oxycodone DETERx Intact HFHC	Oxycodone DETERx Crushed HFHC	OxyContin Intact HFHC	OxyContin Crushed HFHC	IR Oxycodone Crushed HFHC
Tlag (h)	0.88 (38)	0.50 (39)	0.50 (38)	0.25 (39)	0.25 (37)
	[0.50 – 1.75]	[0.25 – 1.00]	[0.25 – 1.00]	[0.25 – 0.50]	[0.25 – 0.50]
Cmax (ng/mL)	56.9 ± 13.4 (38)	61.2 ± 13.1 (39)	63.7 ± 14.8 (38)	79.9 ± 17.9 (39)	78.1 ± 22.0 (37)
Tmax (h)	3.50 (38)	3.50 (39)	4.51 (38)	1.75 (39)	1.50 (37)
	[1.00 05.5]	[2.50 5.50]	[1.75 8.00]	[0.50 4.50]	[0.50 4.53]
AUC(0-t) (hr×ng/mL)	517 + 145 (38)	539 + 144 (39)	566 + 150 (38)	531 + 141 (39)	487 + 137 (37)
AUC(inf) (hr×ng/mL)	534 + 142 (37)	549 + 143 (39)	574 + 150 (38)	540 + 142 (39)	497 + 143 (37)
λz (1/h)	0.1260 ± 0.0221 (37)	0.1404 ± 0.0184 (39)	0.1705 ± 0.0254 (38)	0.1733 ± 0.0307 (39)	0.1887 ± 0.0335 (37)
$t_{1/2}$ (h)	5.68 ± 1.12 (37)	5.02 ± 0.63 (39)	4.15 ± 0.59 (38)	4.13 ± 0.76 (39)	3.78 ± 0.66 (37)
CL/F (L/h)	72.7 ± 23.6 (37)	70.0 ± 19.6 (39)	66.9 ± 18.9 (38)	71.6 ± 21.5 (39)	82.8 ± 44.9 (37)
Vz/F (L)	597 ± 235 (37)	503 ± 145 (39)	393 ± 94.3 (38)	416 ± 110 (39)	430 ± 174 (37)
Fr (%)	120 + 93.2 (35)	126 + 100 (36)	130 + 104 (36)	124 + 100 (37)	†

*Arithmetic mean + standard deviation (N) except T_{lag} and T_{max} for which the median (N) [Range] is reported.
†Not applicable as IR Oxycodone Crushed HFHC was the reference treatment.

CV = coefficient of variation; Extrap = Extrapolated; HFHC = high-fat, high-caloric; IR = immediate-release; Max = maximum; Min = minimum; n = number of subject used in the calculation; NA = not applicable; PK = pharmacokinetic; SD = standard deviation

Source: Appendix 16.6.1, Table 2

Statistical analysis showing bioequivalence comparison of oxycodone Cmax, AUC parameters is presented in the table below. The sponsor conducted primary comparisons with oral IR oxycodone 40 mg as reference; however, secondary analysis comparisons with intact Xtampza taken with food were also used in the review. In this study, conducted under fed-state, the peak plasma levels of oral OxyContin fed (Oxycodone extended-release tablets) administered after crushing resulted in 25% higher plasma levels at median Tmax of 1.75 hours compared to intact OxyContin fed (Oxycodone extended-release tablets) taken orally with a Tmax of 4.5 hours. According to the bioequivalence analysis using IR oxycodone crushed taken with food as reference,

a) Crushed Xtampza has 20% lower Cmax compared to IR, overall AUC is comparable across treatments.
b) Crushed OxyContin fed (Oxycodone extended-release tablets) has similar Cmax and AUC as demonstrated by the 90% CI for geometric mean ratio being within 80 -125%.

Table: BE analysis using crushed IR oxycodone fed as reference in Study CP-OXYDET-29.

Test	Reference	Parameter	LS Geometric Means		LS Geometric Mean Ratio (%)*		Within-Subject CV(%)
			Test	Reference	Estimate	90% Confidence Interval	
Oxycodone DETERx Crushed HFHC	IR Oxycodone Crushed HFHC	Cmax	59.50	74.25	80.13	74.24 → 86.49	20.03
		AUC(0-t)	520.87	458.74	113.54	106.20 → 121.40	17.51
		AUC(inf)	531.44	470.72	112.90	105.76 → 120.51	17.03
OxyContin Crushed HFHC	IR Oxycodone Crushed HFHC	Cmax	77.70	74.25	104.65	97.02 → 112.88	20.03
		AUC(0-t)	508.37	458.74	110.82	103.71 → 118.42	17.51
		AUC(inf)	520.64	470.72	110.60	103.69 → 117.98	17.03

CV = coefficient of variation; LS = least squares; HFHC = high-fat, high-calorie meal; IR = immediate-release.

Source: Listing 8

According to additional bioequivalence type analyses that allow for relative bioavailability comparison,
a) using Intact Xtampza taken with food is bioequivalent to crushed Xtampza is regard to both Cmax and AUC. Even after crushing, Tmax of Xtampza remained at a median of 3.5 hours.
b) using Intact OxyContin fed (Oxycodone extended-release tablets) as reference, intact Xtampza is bioequivalent with regard to Cmax and AUC.

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c) using crushed OxyContin fed (Oxycodone extended-release tablets) as reference, crushed Xtampza has 24% lower Cmax and similar AUC. However, Tmax of crushed OxyContin fed (Oxycodone extended-release tablets) was noted at a median of 1.75 hours compared to 3.5 hours for crushed Xtampza (See table above on page 5).

Table: BE analysis using different treatments (fed) as reference in Study CP-OXYDET-29.

Test	Reference	Parameter	LS Geometric Means		LS Geometric Mean Ratio (%)*		Within-Subject CV (%)
			Test	Reference	Estimate	90% Confidence Interval	
Oxycodone DETERx Crushed HFHC	Oxycodone DETERx Intact HFHC	Cmax	59.50	55.61	106.99	99.23 → 115.35	20.03
		AUC(0-t)	520.87	497.05	104.79	98.11 → 111.93	17.51
		AUC(inf)	531.44	515.35	103.12	96.62 → 110.05	17.03
OxyContin Crushed HFHC	OxyContin Intact HFHC	Cmax	77.70	61.68	125.98	116.85 → 135.83	20.03
		AUC(0-t)	508.37	544.20	93.42	87.46 → 99.78	17.51
		AUC(inf)	520.64	556.95	93.48	87.67 → 99.68	17.03
Oxycodone DETERx Intact HFHC	IR Oxycodone Crushed HFHC	Cmax	55.61	74.25	74.90	69.35 → 80.89	20.03
		AUC(0-t)	497.05	458.74	108.35	101.29 → 115.91	17.51
		AUC(inf)	515.35	470.72	109.48	102.50 → 116.93	17.03
OxyContin Intact HFHC	IR Oxycodone Crushed HFHC	Cmax	61.68	74.25	83.07	76.92 → 89.71	20.03
		AUC(0-t)	544.20	458.74	118.63	110.90 → 126.89	17.51
		AUC(inf)	556.95	470.72	118.32	110.81 → 126.33	17.03
Oxycodone DETERx Intact HFHC	OxyContin Intact HFHC	Cmax	55.61	61.68	90.17	83.58 → 97.27	20.03
		AUC(0-t)	497.05	544.20	91.34	85.46 → 97.61	17.51
		AUC(inf)	515.35	556.95	92.53	86.72 → 98.73	17.03
Oxycodone DETERx Crushed HFHC	OxyContin Crushed HFHC	Cmax	59.50	77.70	76.57	71.04 → 82.53	20.03
		AUC(0-t)	520.87	508.37	102.46	95.94 → 109.41	17.51
		AUC(inf)	531.44	520.64	102.07	95.73 → 108.83	17.03

CV = coefficient of variation; LS = least squares; HFHC = high-fat, high-calorie meal; IR = immediate-release.

Source: Listing 8

In addition, descriptive statistics of cumulative partial AUC's for crushed Xtampza (Oxycodone DETERx) were lower than that noted with crushed OxyContin fed (Oxycodone extended-release tablets) taken orally with food.

Table: Descriptive Statistics of Oxycodone Cumulative Partial AUCs in Study CP-OXYDET-29.

Cumulative PAUC*	Oxycodone DETERx Intact HFHC	Oxycodone DETERx Crushed HFHC	OxyContin Intact HFHC	OxyContin Crushed HFHC	IR Oxycodone Crushed HFHC
PAUC(0-0.25) (hr×ng/mL)	0.00 ± 0.00 (38)	0.06 ± 0.08 (39)	0.07 ± 0.23 (38)	1.03 ± 0.90 (39)	1.56 ± 1.60 (37)
PAUC(0-0.5) (hr×ng/mL)	0.14 ± 0.37 (38)	0.68 ± 0.47 (39)	0.65 ± 1.11 (38)	5.84 ± 4.05 (39)	7.95 ± 6.29 (37)
PAUC(0-0.75) (hr×ng/mL)	0.71 ± 1.62 (38)	2.51 ± 1.45 (39)	2.19 ± 2.90 (38)	15.20 ± 8.69 (39)	19.62 ± 12.83 (37)
PAUC(0-1) (hr×ng/mL)	2.27 ± 3.77 (38)	5.73 ± 2.98 (39)	4.64 ± 5.55 (38)	28.08 ± 13.22 (39)	33.97 ± 18.91 (37)
PAUC(0-1.25) (hr×ng/mL)	5.02 ± 6.75 (38)	10.32 ± 5.08 (39)	7.97 ± 8.89 (38)	43.33 ± 17.52 (39)	48.81 ± 23.77 (37)
PAUC(0-1.5) (hr×ng/mL)	9.02 ± 10.33 (38)	16.39 ± 7.58 (39)	12.16 ± 12.53 (38)	59.24 ± 21.34 (39)	64.13 ± 27.69 (37)
PAUC(0-1.75) (hr×ng/mL)	14.67 ± 14.53 (38)	23.80 ± 10.45 (39)	17.20 ± 16.41 (38)	75.60 ± 24.93 (39)	80.01 ± 31.30 (37)
PAUC(0-2) (hr×ng/mL)	21.46 ± 18.85 (38)	32.25 ± 13.43 (39)	23.05 ± 20.58 (38)	92.23 ± 28.31 (39)	96.39 ± 34.68 (37)
PAUC(0-2.5) (hr×ng/mL)	38.24 ± 27.21 (38)	52.74 ± 19.53 (39)	36.85 ± 29.91 (38)	125.56 ± 34.15 (39)	128.51 ± 40.67 (37)
PAUC(0-3) (hr×ng/mL)	58.27 ± 34.53 (38)	77.23 ± 25.64 (39)	53.20 ± 39.19 (38)	158.20 ± 39.23 (39)	159.26 ± 46.04 (37)
PAUC(0-3.5) (hr×ng/mL)	80.10 ± 40.62 (38)	103.64 ± 30.76 (39)	72.33 ± 47.67 (38)	189.48 ± 43.72 (39)	188.69 ± 51.32 (37)
PAUC(0-4) (hr×ng/mL)	103.28 ± 45.62 (38)	130.71 ± 35.46 (39)	93.83 ± 54.99 (38)	218.66 ± 48.49 (39)	216.07 ± 56.58 (37)
PAUC(0-4.5) (hr×ng/mL)	127.59 ± 49.36 (38)	157.97 ± 39.86 (39)	118.46 ± 60.81 (38)	246.18 ± 53.53 (39)	241.36 ± 61.49 (37)
PAUC(0-5) (hr×ng/mL)	151.75 ± 51.93 (38)	184.33 ± 43.39 (39)	145.37 ± 64.77 (38)	271.43 ± 58.56 (39)	263.99 ± 65.97 (37)
PAUC(0-5.5) (hr×ng/mL)	173.97 ± 54.18 (38)	208.45 ± 46.88 (39)	171.75 ± 67.56 (38)	293.41 ± 63.44 (39)	†
PAUC(0-6) (hr×ng/mL)	194.86 ± 56.56 (38)	231.10 ± 50.22 (39)	198.09 ± 70.92 (38)	313.56 ± 68.05 (39)	302.32 ± 73.56 (37)
PAUC(0-7) (hr×ng/mL)	231.62 ± 63.26 (38)	270.43 ± 58.14 (39)	246.87 ± 75.66 (38)	347.03 ± 75.96 (39)	†
PAUC(0-8) (hr×ng/mL)	264.39 ± 69.71 (38)	305.23 ± 66.00 (39)	292.67 ± 79.75 (38)	375.26 ± 82.84 (39)	360.29 ± 88.41 (37)
PAUC(0-9) (hr×ng/mL)	293.52 ± 75.62 (38)	335.34 ± 73.19 (39)	332.68 ± 83.91 (38)	398.81 ± 89.03 (39)	†
PAUC(0-10) (hr×ng/mL)	319.24 ± 81.46 (38)	361.18 ± 80.06 (39)	366.19 ± 88.02 (38)	418.43 ± 94.82 (39)	†
PAUC(0-12) (hr×ng/mL)	360.64 ± 92.48 (38)	401.46 ± 92.06 (39)	416.31 ± 96.76 (38)	447.76 ± 104.34 (39)	429.35 ± 110.03 (37)
PAUC(0-16) (hr×ng/mL)	†	†	†	†	460.55 ± 122.70 (37)
PAUC(0-24) (hr×ng/mL)	488.69 ± 132.43 (38)	520.57 ± 131.35 (39)	552.92 ± 137.12 (38)	526.27 ± 135.59 (39)	486.76 ± 137.03 (37)
PAUC(0-36) (hr×ng/mL)	516.72 ± 144.65 (38)	539.33 ± 143.96 (39)	566.02 ± 150.07 (38)	530.95 ± 140.69 (39)	†

*Arithmetic mean ± standard deviation (N)
†Sample time not applicable to the treatment.
HFHC = high-fat, high-calorie meal; IR = immediate-release.

Source: Listing 10

Reference ID: 4161285

The above results indicate that Category 2 PK Study CP-OXYDET-29 replicated the findings of Category 2 PK Study CP-OXYDET-25. The sponsor proposed a labeling claim based on the results of these studies (See section 2.1 of the review).

PK results from Category 3 human abuse potential study CP-OXYDET-28:

The abuse potential (PD) results from study CP-OXYDET-28 can be found in reviews by Dr. Anna Sun and Dr. James Tolliver. This study is a randomized, double-blind, active- and placebo-controlled, single-dose, six-way crossover pharmacodynamic study, where 52 non-dependent recreational opioid users received orally-administered active and placebo treatment. The six treatment arms were intact XTAMPZA ER (36 mg, fed or HFHC and fasted); chewed XTAMPZA ER (36 mg, fed or HFHC and fasted); crushed immediate-release (IR) oxycodone HCl in solution (40 mg, fasted, equivalent to 36 mg of XTAMPZA ER), and placebo.

Mean oxycodone Cmax was for crushed IR oxycodone fasted was 91.1 (SD= 26.6) ng/mL. Xtampza treatments, intact and chewed Xtampza fed treatments had higher Cmax (45.4 ± 11.6 ng/mL and 44.3 ± 10.9 ng/mL, respectively) compared with the intact and chewed Xtampza fasted treatments (33.9 ± 9.79 ng/mL and 37.6 ± 11.5 ng/mL, respectively). Median Tmax was earliest for crushed IR oxycodone fasted (0.54 hour), followed by the Xtampza fasted treatments (3.07-4.05 hours), and latest for the Xtampza fed treatments (5.07 hours). Both AUC(0-t) and AUC(inf) values were generally comparable for crushed IR oxycodone fasted and crushed Xtampza fed treatments (541-568 h*ng/mL), whereas exposure was slightly lower for the Xtampza fasted treatments (447-480 h*ng/mL). This observation is very consistent with the previously known food-effect.

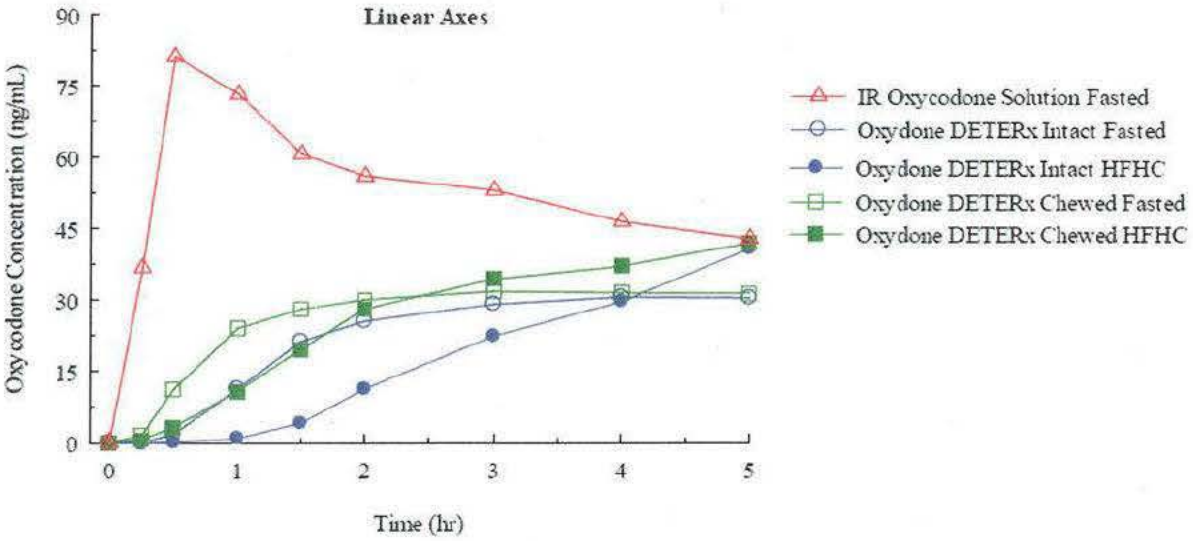
Table: Descriptive Statistics of Oxycodone PK Parameters in Study CP-OXYDET-28.

Parameter*	Oxycodone DETERx Intact HFHC	Oxycodone DETERx Intact Fasted	Oxycodone DETERx Chewed HFHC	Oxycodone DETERx Chewed Fasted	IR Oxycodone Solution Fasted
Tlag (hr)	1.55 (61) [0.55 – 4.07]	0.55 (67) [0.30 – 3.07]	0.53 (66) [0.30 – 1.08]	0.30 (67) [0.30 – 0.57]	0.30 (64) [0.30 – 0.38]
Cmax (ng/mL)	45.4 ± 11.6 (61)	33.9 ± 9.79 (67)	44.3 ± 10.9 (66)	37.6 ± 11.5 (67)	91.1 ± 26.6 (64)
Tmax (hr)	5.07 (61) [2.07 – 12.1]	4.05 (67) [1.52 – 8.07]	5.07 (66) [1.52 – 8.07]	3.07 (67) [0.53 – 8.07]	0.54 (64) [0.30 – 5.15]
AUC(0-t) (hr×ng/mL)	541 ± 127 (61)	447 ± 119 (67)	553 ± 149 (66)	466 ± 145 (67)	543 ± 131 (64)
AUC(inf) (hr×ng/mL)	546 ± 134 (52)	478 ± 122 (63)	568 ± 138 (54)	480 ± 126 (63)	549 ± 132 (63)
λz (1/hr)	0.1332 ± 0.0184 (52)	0.0918 ± 0.0231 (63)	0.1303 ± 0.0171 (54)	0.0993 ± 0.0256 (63)	0.1679 ± 0.0226 (63)
$t^{1}/_{2}$ (hr)	5.30 ± 0.74 (52)	8.14 ± 2.47 (63)	5.42 ± 0.79 (54)	7.57 ± 2.50 (63)	4.21 ± 0.58 (63)
CL/F (L/hr)	69.7 ± 17.3 (52)	80.0 ± 21.0 (63)	67.1 ± 17.0 (54)	79.9 ± 21.1 (63)	69.2 ± 17.0 (63)
Vz/F (L)	528 ± 131 (52)	944 ± 388 (63)	516 ± 112 (54)	874 ± 379 (63)	411 ± 80.3 (63)
Fr (%)	102 ± 15.2 (48)	88.2 ± 21.3 (55)	106 ± 14.2 (49)	89.6 ± 18.3 (59)	†

*Arithmetic mean ± standard deviation (N) except Tlag and Tmax for which the median (N) [Range] is reported.
†Not applicable as IR Oxycodone Solution Fasted was the reference treatment.
HFHC = high-fat, high-calorie meal; IR = immediate-release; PK = pharmacokinetic.

Source: Listing 9.

Figure: Mean Oxycodone PK Profile, Over First Five Hours for Emphasis, in Study CP-OXYDET-28)



Intact Xtampza fed has 50% lower Cmax, and Xtampza fasted has 63% lower Cmax compared to oral solution prepared from IR crushed formulation fasted. Chewed Xtampza fed has 50% lower Cmax, and chewed Xtampza fasted has 59% lower Cmax compared to oral solution from IR crushed formulation fasted.

Table: BE Analysis Using Crushed IR Oxycodone Fed as Reference in Study CP-OXYDET-28.

Test	Reference	Parameter	LS Geometric Means		LS Geometric Mean Ratio (%)*				Within-Subject CV (%)
			Test	Reference	Estimate	90% Confidence Interval			
Oxycodone DETERx Intact HFHC	IR Oxycodone Solution Fasted	Cmax	44.92	87.97	51.06	48.03	→	54.28	20.61
		AUC(0-t)	528.13	525.29	100.54	95.08	→	106.32	18.78
		AUC(inf)	546.57	534.29	102.30	97.82	→	106.99	14.12
Oxycodone DETERx Intact Fasted	IR Oxycodone Solution Fasted	Cmax	32.71	87.97	37.19	35.03	→	39.48	20.61
		AUC(0-t)	423.68	525.29	80.66	76.38	→	85.18	18.78
		AUC(inf)	461.97	534.29	86.46	82.87	→	90.21	14.12
Oxycodone DETERx Chewed HFHC	IR Oxycodone Solution Fasted	Cmax	43.14	87.97	49.05	46.21	→	52.06	20.61
		AUC(0-t)	525.90	525.29	100.12	94.81	→	105.72	18.78
		AUC(inf)	554.08	534.29	103.70	99.22	→	108.39	14.12
Oxycodone DETERx Chewed Fasted	IR Oxycodone Solution Fasted	Cmax	36.24	87.97	41.19	38.84	→	43.69	20.61
		AUC(0-t)	447.65	525.29	85.22	80.77	→	89.92	18.78
		AUC(inf)	469.51	534.29	87.88	84.31	→	91.60	14.12

AUC(0-t) = area under the plasma concentration-time curve from 0 to the final time with a concentration ≥ LOQ; AUC(inf) = area under the plasma concentration-time curve to infinity; Cmax = maximum plasma concentration; CV = coefficient of variation; LS = least squares; HFHC = high-fat, high-calorie meal; IR = immediate-release; LOQ = validated lower limit of the bioanalytical method; PK = pharmacokinetic.

Source: Listing 11.

As seen in the table below, when compared to intact Xtampza fed, both crushed Xtampza fed and crushed Xtampza fasted had similar Cmax. Xtampza when taken under fasted-state has 27% low Cmax compared to fed-state. Xtampza taken fasted after chewing still has 16% lower Cmax compared to Xtampza taken fed after chewing.

Table: BE Analysis Using Different Treatments (fed) as Reference in Study CP-OXYDET-28.

Test	Reference	Parameter	LS Geometric Means		LS Geometric Mean Ratio (%)*		Within-Subject CV(%)
			Test	Reference	Estimate	90% Confidence Interval	
Oxycodone DETERx Intact Fasted	Oxycodone DETERx Intact HFHC	Cmax	32.71	44.92	72.83	68.56 → 77.37	20.61
		AUC(0-t)	423.68	528.13	80.22	75.92 → 84.77	18.78
		AUC(inf)	461.97	546.57	84.52	80.82 → 88.40	14.12
Oxycodone DETERx Chewed Fasted	Oxycodone DETERx Chewed HFHC	Cmax	36.24	43.14	83.99	79.20 → 89.07	20.61
		AUC(0-t)	447.65	525.90	85.12	80.68 → 89.81	18.78
		AUC(inf)	469.51	554.08	84.74	81.07 → 88.57	14.12
Oxycodone DETERx Chewed HFHC	Oxycodone DETERx Intact HFHC	Cmax	43.14	44.92	96.06	90.37 → 102.11	20.61
		AUC(0-t)	525.90	528.13	99.58	94.18 → 105.29	18.78
		AUC(inf)	554.08	546.57	101.37	96.71 → 106.26	14.12
Oxycodone DETERx Chewed Fasted	Oxycodone DETERx Intact Fasted	Cmax	36.24	32.71	110.77	104.44 → 117.48	20.61
		AUC(0-t)	447.65	423.68	105.66	100.13 → 111.49	18.78
		AUC(inf)	469.51	461.97	101.63	97.43 → 106.02	14.12
Oxycodone DETERx Chewed Fasted	Oxycodone DETERx Intact HFHC	Cmax	36.24	44.92	80.68	75.93 → 85.72	20.61
		AUC(0-t)	447.65	528.13	84.76	80.20 → 89.59	18.78
		AUC(inf)	469.51	546.57	85.90	82.12 → 89.85	14.12

AUC(0-t) = area under the plasma concentration-time curve from 0 to the final time with a concentration ≥ LOQ; AUC(inf) = area under the plasma concentration-time curve to infinity; Cmax = maximum plasma concentration; CV = coefficient of variation; LS = least squares; HFHC = high-fat, high-calorie meal; IR = immediate-release; LOQ = validated lower limit of the bioanalytical method; PK = pharmacokinetic.

Source: Listing 11.

Table: Descriptive Statistics of Oxycodone Cumulative Partial AUCs in Study CP-OXYDET-28.

Cumulative PAUC*	Oxycodone DETERx Intact HFHC	Oxycodone DETERx Intact Fasted	Oxycodone DETERx Chewed HFHC	Oxycodone DETERx Chewed Fasted	IR Oxycodone Solution Fasted
PAUC(0-0.25) (hr×ng/mL)	0.00 ± 0.00 (61)	0.00 ± 0.03 (67)	0.10 ± 0.21 (66)	0.24 ± 0.31 (67)	5.62 ± 4.81 (64)
PAUC(0-0.5) (hr×ng/mL)	0.00 ± 0.02 (61)	0.21 ± 0.31 (67)	0.56 ± 0.85 (66)	1.73 ± 1.71 (67)	19.73 ± 12.40 (64)
PAUC(0-1) (h×ng/mL)	0.24 ± 0.61 (61)	3.47 ± 2.33 (67)	4.07 ± 3.74 (66)	10.57 ± 7.27 (67)	57.83 ± 22.30 (64)
PAUC(0-1.5) (hr×ng/mL)	1.51 ± 2.51 (61)	11.57 ± 5.14 (67)	11.66 ± 8.25 (66)	23.56 ± 12.69 (67)	91.63 ± 30.33 (64)
PAUC(0-2) (hr×ng/mL)	5.59 ± 7.26 (61)	24.02 ± 8.31 (67)	24.48 ± 13.53 (66)	39.03 ± 17.29 (67)	122.48 ± 38.47 (64)
PAUC(0-3) (hr×ng/mL)	22.38 ± 21.39 (61)	51.29 ± 14.31 (67)	55.72 ± 23.41 (66)	70.00 ± 24.60 (67)	177.06 ± 50.58 (64)
PAUC(0-4) (hr×ng/mL)	48.49 ± 36.19 (61)	81.25 ± 20.96 (67)	91.39 ± 31.70 (66)	101.64 ± 31.71 (67)	226.89 ± 59.46 (64)
PAUC(0-5) (hr×ng/mL)	83.76 ± 46.77 (61)	111.75 ± 29.33 (67)	130.36 ± 39.44 (66)	133.27 ± 38.85 (67)	271.54 ± 66.13 (64)
PAUC(0-6) (hr×ng/mL)	122.13 ± 53.95 (61)	141.10 ± 37.39 (67)	168.90 ± 47.83 (66)	163.23 ± 45.89 (67)	310.28 ± 71.74 (64)
PAUC(0-8) (hr×ng/mL)	191.73 ± 64.47 (61)	189.89 ± 58.35 (67)	236.33 ± 62.67 (66)	216.74 ± 59.43 (67)	370.04 ± 80.41 (64)
PAUC(0-12) (hr×ng/mL)	309.88 ± 73.93 (61)	271.75 ± 75.25 (67)	344.56 ± 84.49 (66)	297.73 ± 82.20 (67)	448.45 ± 96.50 (64)
PAUC(0-24) (hr×ng/mL)	500.70 ± 110.00 (61)	400.74 ± 110.78 (67)	514.34 ± 127.33 (66)	423.92 ± 125.75 (67)	536.43 ± 124.03 (64)
PAUC(0-36) (hr×ng/mL)	541.31 ± 127.46 (61)	446.58 ± 118.61 (67)	552.84 ± 148.89 (66)	466.47 ± 144.82 (67)	542.72 ± 130.64 (64)

*Arithmetic mean ± standard deviation (N).
HFHC = high-fat, high-calorie meal; IR = immediate-release; PAUC = partial area under the plasma concentration-time curve; PK = pharmacokinetic.

Source: Listing 13.

Reference ID: 4161285

Table: Descriptive Statistics of Oxycodone Cumulative Partial AUEs in Study CP-OXYDET-28.

PD Parameter	Intact Oxycodone DETERx HFHC	Intact Oxycodone DETERx Fasted	Chewed Oxycodone DETERx HFHC	Chewed Oxycodone DETERx Fasted	Crushed IR Oxycodone Fasted	Placebo HFHC
$AUE_{0\text{-}1h}$ (h·pts)						
Mean (SD)	2.9 (7.70)	3.2 (6.94)	2.4 (3.82)	4.6 (5.35)	17.9 (9.25)	2.0 (3.99)
Median	0.0	0.4	0.7	2.5	17.0	0.0
$AUE_{0\text{-}2h}$ (h·pts)						
Mean (SD)	8.9 (16.74)	14.7 (16.87)	10.6 (13.22)	20.1 (15.57)	47.3 (20.30)	5.0 (9.05)
Median	2.4	9.6	5.9	18.3	50.9	0.0
$AUE_{0\text{-}4h}$ (h·pts)						
Mean (SD)	33.7 (37.37)	47.1 (41.14)	40.4 (33.20)	53.6 (39.24)	93.2 (44.35)	7.8 (15.31)
Median	23.8	41.3	35.9	55.0	94.2	0.0
$AUE_{0\text{-}8h}$ (h·pts)						
Mean (SD)	103.6 (90.66)	104.6 (93.25)	107.8 (84.12)	102.4 (85.48)	154.6 (91.40)	9.5 (19.15)
Median	97.8	94.7	85.0	80.5	136.3	0.0
$AUE_{0\text{-}24h}$ (h·pts)						
Mean (SD)	240.8 (264.84)	190.3 (197.24)	204.6 (211.08)	167.8 (193.14)	220.9 (170.17)	4.8 (63.70)
Median	196.8	117.0	137.3	103.1	164.8	0.0
TE_{max} (h)						
Median	4.0	3.0	4.0	2.0	1.0	0.3
Min, Max	0, 8	0, 8	0, 8	0, 8	0, 8	0, 3
E_{min} (pts)						
Mean (SD)	48.2 (11.93)	48.7 (6.78)	48.3 (7.60)	49.1 (7.04)	49.6 (1.47)	48.8 (6.93)
Median	50.0	50.0	50.0	50.0	50.0	50.0
TE_{min} (h)						
Median	0.3	0.3	0.3	0.3	0.3	0.3
Min, Max	0, 24	0, 24	0, 24	0, 24	0, 24	0, 24

$AUE_{0\text{-}xh}$ = area under the effect curve from time zero to x hours post-dose; E_{max} = maximum (peak) effect; E_{min} = minimum effect; h = hour; HFHC = high-fat, high-calorie; IR = immediate-release; Max = maximum; Min = minimum; PD = pharmacodynamic; pts = points; SD = standard deviation; TE_{max} = time to maximum (peak) effect; TE_{min} = time to minimum effect; VAS = visual analog scale

Data Source: Table 14.2.1-2

Reference ID: 4161285

2.1 Summary of Labeling Recommendations

The sponsor wants to describe the PK of Xtampza after oral abuse in relation to OxyContin (Oxycodone extended-release tablets) in Section 9 of the product label. The proposed table is acceptable since the results have been replicated in studies CP-OXYDET-25 and CP-OXYDET-29. Also the sponsor wants description of human abuse potential in terms of "drug liking" and "Take Drug Again" for Xtampza after oral abuse compared to immediate release and intact Xtampza.

Table 3: Oxycodone Pharmacokinetic Parameters, Administration of (b) (4)

	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-INF} (hr•ng/mL)
Treatment	**Oral Pharmacokinetic Study 1**		
Intact XTAMPZA ER Capsules (fed)	62.3 (13.0)	4.0 (1.5-6)	561 (124)
Crushed XTAMPZA ER Capsule Contents (fed)	57.6 (12.6)	4.5 (2.5-6)	553 (134)
Chewed XTAMPZA ER Capsule Contents (fed)	55.6 (10.9)	4.5 (2.5-8)	559 (113)	
Immediate-Release Oxycodone Solution (fasted)	115 (27.3)	0.75 (0.5-2)	489 (80.2)
	Oral Pharmacokinetic Study 2		
Intact XTAMPZA ER Capsules (fed)	67.5 (17.6)	3.5 (1.25 – 6.0)	581 (138)
Crushed XTAMPZA ER Capsule Contents (fed)	62.9 (12.6)	4.0 (2.0 – 7.0)	597 (149)
Intact (b) (4) Tablets (fed)	64.9 (13.8)	5.0 (2.0-10.0)	611 (145)
Crushed (b) (4) Tablets (fed)	78.4 (12.9)	1.75 (0.5-5.0)	587 (132)
Crushed Immediate-Release Oxycodone Tablets (fed)	79.4 (17.1)	1.75 (0.5-4.0)	561 (146)

Values shown for C_{max} and AUC_{0-INF} are mean (standard deviation); values shown for T_{max} are median (minimum-maximum).

3. APPENDICES

[Please note: The appendices listed below are examples only; appendices should be tailored to the review of a particular submission.]

3.1 Summary of Bioanalytical Method Validation and Performance

The determination of plasma oxycodone concentrations was performed by (b) (4) Assays were conducted in compliance with (b) (4) Standard Operation Procedures in accordance with applicable Good Laboratory Practice regulations (21 CRF 58) and FDA's May 2001 Guidance for Industry, Bioanalytical Method Validation. The analytical method is documented in a Method Validation report. All documents referenced are on file at (b) (4) The results were provided in a Bioanalytical Report entitled "An Evaluation of the Effect of Tampering on Oxycodone DETERx® Compared with OxyContin®, LC-MS/MS Determination of Oxycodone in Human Plasma (K2EDTA)", dated 01 June 2014, provided by (b) (4) The individual study bioanalytical reports were also provided and reviewed and found acceptable.

Report Number	Report Title
(b) (4)	LC-MS/MS Determination of Oxycodone in Human Plasma (K_2EDTA) "An Evaluation of the Effect of Tampering on Oxycodone DETERx® Compared with OxyContin®" Collegium Pharmaceutical. Inc. Protocol CP-OXYDET-29, Report Date 26-May-2016

All samples for a given subject were analyzed together in a single batch except when samples had to be reassayed.

Batch Acceptance Criteria

- Standards were rejected if they were greater than ± 15% (all standards but the LLOQ) or ± 20% (LLOQ only) of the nominal concentration.
- At least 75% of the non-zero standards were within the respective acceptance criterion.
- At least two-thirds of the low, medium, and high QCs, including at least 50% at each concentration, were valid data points and were within ± 15% of the nominal concentration.

Between-batch precision and accuracy results for QC samples prepared at low, medium, and high QC concentrations was acceptable. The accuracy of sample dilution was verified by the performance of dilution QC samples. At least 50% of the diluted QC samples (denoted with the dilution factor following the QC identifier) had to be within ± 15% of the nominal concentration for the dilution scheme to be accepted. Standard curve parameters from 42 successful analytical batches were provided. Selectivity evaluations performed during the validation can be found in method validation report ZZ37950-01 (see Table below). To demonstrate that the analysis of incurred sample concentrations were reproducible for the bioanalytical method, 281 study samples were reassayed. The results demonstrate that 99.3% of the pairs matched and that the method is considered reproducible.

Reference ID: 4161285

Report Number	Report Title
(b) (4)	LC-MS/MS Determination of Oxycodone in Human Plasma (K2EDTA) "Assessment of the Oral Human Abuse Liability and Pharmacokinetics of Oxycodone DETERx®" Collegium Pharmaceutical, Inc. Protocol CP-OXYDET-28, Report Date 01-Feb-2017.

For Study CP-OXYDET-28, all samples for a given subject were analyzed together in a single batch except when samples had to be reassayed. Batch Acceptance Criteria

- Standards were rejected if they were greater than ± 15% (all standards but the LLOQ) or ± 20% (LLOQ only) of the nominal concentration.
- At least 75% of the non-zero standards were within the respective acceptance criterion.
- At least two-thirds of the low, medium, and high QCs, including at least 50% at each concentration, were valid data points and were within ± 15% of the nominal concentration.

Between-batch precision and accuracy results for QC samples prepared at low, medium, and high QC concentrations was acceptable. The accuracy of sample dilution was verified by the performance of dilution QC samples. Standard curve parameters from 38 successful analytical batches are provided. To demonstrate that the analysis of incurred sample concentrations were reproducible for the bioanalytical method, 312 study samples were reassayed. Results demonstrate that 99.4% of the pairs matched and that the method is considered reproducible.

Table: Validation Summary	(b) (4) Validation Study ZZ37950-01
Analyte	Oxycodone
Internal Standard (IS)	(b) (4)
Method Description	Solid phase extraction with analysis/detection by LC-MS/MS
Limit of Quantitation (ng/mL)	0.500 ng/mL
Average Recovery of Drug (% Mean)	57% at 1.20 ng/mL 66% at 15.0 ng/mL 62% at 75.0 ng/mL
Average Recovery of IS (% Mean)	61%
Standard Curve Concentrations (ng/mL)	0.500, 1.00, 2.00, 5.00, 10.0, 20.0, 50.0, 80.0, and 100 ng/mL
QC Concentrations (ng/mL)	LLOQ QC, 1.20, 15.0, and 75.0 ng/mL
QC Intra-Batch Precision Range (% CV)	0.8 to 4.9%
QC Intra-Batch Accuracy Range (% Bias)	-1.6 to 14.7%
QC Inter-Batch Precision Range (% CV)	3.3 to 5.3%
QC Inter-Batch Accuracy Range (% Bias)	3.2 to 9.3%
Bench-Top Stability (Hrs)	Short-Term Stability: 24 hours in polypropylene tubes at ambient temperature under white light Cumulative Short-Term Stability: 51 hours in polypropylene tubes at ambient temperature under white light (total of all thaw cycles)
Stock Stability (Days)	Long-Term Stability for Stock Solutions (Stock): 231 days at approximately 1000 µg/mL in methanol in polypropylene at -20°C

Reference ID: 4161285

Processed Stability (Hrs)	Post-Preparative Stability: 154 hours in a polypropylene 96 well plate at 5°C Processed Sample Integrity: 182 hours in a polypropylene 96 well plate at 5°C
Freeze-Thaw Stability (Cycles)	6 freeze (-20°C)-thaw (ambient temperature) cycles in polypropylene tubes under white light
Long-Term Storage Stability (Days)	Long-Term Stability: 706 days in polypropylene tubes at -20°C
Dilution Integrity	Up to 300 ng/mL, diluted 5-fold
Selectivity	No significant interference at the retention time and mass transition of oxycodone was observed from endogenous components in any of the 6 human plasma (EDTA) lots screened or of (b) (4) (IS) in any of the 6 human plasma (EDTA) lots screened
Matrix	Human Plasma
Anticoagulant	K2EDTA
Bioanalytical Method (BAM) SOP Number	BAM SOP ZZ37950-01
Detector	(b) (4)
Assay Volume Required	0.100 mL
Regression Type	Weighted linear (1/concentration2)
Quantitation Method	Peak area ratio
Co-administered Compound Evaluation	Ondansetron (500 ng/mL)
Over-the-Counter Cocktail Testing	Acetaminophen (25.0 µg/mL) Atorvastatin (100 ng/mL) Caffeine (20.0 µg/mL) Cetirizine (500 ng/mL) Dextromethorphan (25.0 ng/mL) Ethinyl Estradiol (0.500 ng/mL) Famotidine (200 ng/mL) Ibuprofen (20.0 µg/mL) Levonorgestrel (5.00 ng/mL) Metformin (2.00 µg/mL) Omeprazole (300 ng/mL) Ondansetron (200 ng/mL)
Additional Selectivity Compounds	Morphine (10.0 ng/mL) (b) (4) (b) (4) (b) (4) Acetaminophen (1000 ng/mL) Naloxone (1000 ng/mL) Naltrexone (10.0 ng/mL)

Quality Control Samples		Precision (% CV)	Accuracy (% Bias)
Inter-Batch	**LLOQ**	3.3	3.2
	Low	4.7	5.8
	Medium	5.3	9.3
	High	5.2	3.7
Intra-Batch (Batch 3) [1]	**LLOQ**	1.7	4.2
Aliquot Method: Manual	**Low**	4.9	9.2
Extraction Method: Automated	**Medium**	2.0	14.7
	High	3.7	8.8
Intra-Batch (Batch 4)	**LLOQ**	2.8	6.4
Aliquot Method: Manual	**Low**	4.3	9.2
Extraction Method: Automated	**Medium**	0.8	14.0
	High	2.1	7.5
Intra-Batch (Batch 6)	**LLOQ**	3.0	2.0
Aliquot Method: Manual	**Low**	2.2	2.5
Extraction Method: Automated	**Medium**	3.4	3.3
	High	3.3	-1.6
Intra-Batch (Batch 7)	**LLOQ**	3.1	0.6
Aliquot Method: Manual	**Low**	2.1	2.5
Extraction Method: Automated	**Medium**	2.4	4.7
	High	1.5	0.0
Matrix Effect		No significant matrix effect was observed in 4 of the 6 human plasma (EDTA) lots that were fortified with oxycodone at the concentration of the LLOQ (0.500 ng/mL) or in any of the 6 human plasma (EDTA) lots that were fortified with oxycodone at the concentration of the high QC (75.0 ng/mL) samples	
Hemolyzed Sample Integrity		No significant interference for oxycodone was observed in any of the 3 hemolyzed human plasma (EDTA) lots (fortified with 2% whole blood) that were fortified at the concentration of the LLOQ (0.500 ng/mL) or in any of the 3 hemolyzed human plasma (EDTA) lots (fortified with 2% whole blood) that were fortified at the concentration of the high QC (75.0 ng/mL) samples	
Lipemic Sample Evaluation		No significant interference for oxycodone was observed in any of the 3 lipemic human plasma (EDTA) lots that were fortified at the concentration of the LLOQ (0.500 ng/mL) or in any of the 3 lipemic human plasma (EDTA) lots that were fortified at the concentration of the high QC (75.0 ng/mL) samples	
Sample Shipping Stability		7 days in polypropylene tubes at -80°C	
Long-Term Stability for Stock Solutions (Substock)		70 days at 25.0 µg/mL in methanol in polypropylene tubes at -20°C 211 days at 5.00 ng/mL in methanol in polypropylene tubes at -20°C	

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Long-Term Stability for Stock Solutions (Internal Standard)	Refer to long-term stability for stock solutions data collected from unlabeled oxycodone for labeled internal standard stability
Short-Term Stability for Stock Solutions (Substock)	21 hours at approximately 25.0 µg/mL in methanol in a polypropylene contianer at ambient temperature under white light 21 hours at 5.00 ng/mL in methanol in a polypropylene container at ambient temperature under white light
Short-Term Stability for Stock Solutions (Internal Standard)	Refer to short-term stability for stock solutions data collected from unlabeled oxycodone for labeled internal standard stability
Stability of Analyte During Sample Collection and Handling	Up to 120 minutes in human whole blood (EDTA) in polypropylene tubes at ambient temperature under UV-shielded light
Sample Aliquot Frozen Storage Stability	Samples aliquoted manually at a volume of 0.100 mL, stored for 164 hours in a polypropylene 96 well plate at -20°C prior to extraction
Automated Sample Aliquot Integrity	Samples aliquoted using automation at 0.100 mL, extracted after aliquot completion
Batch Size	192 injections

3.2 Clinical PK and/or PD Assessments

3.2.1 Synopsis of Study CP-OXYDET-29:

Title of the Study: An Evaluation of the Effect of Tampering on Oxycodone DETERx® Compared with OxyContin®	
Principal Investigator: Gregory Tracey, MD	
Study Center: Frontage Clinical Services Clinical Research Center 200 Meadowlands Parkway Secaucus, New Jersey 07094 USA	
Publications (reference): None	
Studied Period: 19 January 2016 to 15 March 2016	**Clinical Phase**: I
Objective The objective of this study was to assess the safety and pharmacokinetics (PK) of Oxycodone DETERx intact and crushed in the fed state relative to OxyContin intact and crushed in the fed state and an immediate-release (IR) formulation of oxycodone crushed in the fed state.	
Study Rationale This study was designed to evaluate the impact of tampering on the PK of Oxycodone DETERx compared with a currently marketed extended-release (ER) abuse-deterrent formulation (ADF) of oxycodone – OxyContin – in healthy, naltrexone-blocked subjects using the most aggressive tampering method.	
Number of Subjects Planned and Analyzed The study planned to enroll up to 42 healthy, non-smoking adult male and female volunteer subjects between the ages of 18 and 50 to ensure a minimum of 36 subjects completing the study; 42 subjects were enrolled and randomized to treatment; 35 subjects completed the study and received all planned doses of study drug. Seven (7) subjects (16.7%) discontinued prematurely.	
Methodology This was an open-label, randomized, active-controlled, 5-treatment, 5-period, naltrexone-blocked cross-over comparison study. The study consisted of a Screening Phase and an Open-label Treatment Phase consisting of 5 Treatment Periods with one study drug treatment administered in each Treatment Period. All treatments were administered in the fed state, following a standard high-fat, high-calorie (HFHC) meal.	

Reference ID: 4161285

Subjects were to be screened no more than 14 and no fewer than 2 days prior to initial dosing on Day 1. After providing informed consent, subjects were screened at Visit 1 to determine eligibility and to establish baseline characteristics, as outlined in Table 9-3. Subjects returned to the clinic on the evening prior to study drug dosing for each of the 5 Treatment Periods (Days -1, 5, 10, 15 and 20 based on a 5-day washout between doses).

Subjects were randomized to receive each of 5 treatments in random order, according to a schedule prepared before the start of the study. The 5 treatments, abbreviated A, B, C, D and E, are shown below.

Treatments

- A: Intact Oxycodone DETERx with HFHC Meal (herein "Oxycodone DETERx Intact HFHC")
- B: Crushed Oxycodone DETERx with HFHC Meal (herein "Oxycodone DETERx Crushed HFHC")
- C: Intact OxyContin with HFHC Meal (herein "OxyContin Intact HFHC")
- D: Crushed OxyContin with HFHC Meal (herein "OxyContin Crushed HFHC")
- E: Crushed IR oxycodone with HFHC Meal (herein "IR Oxycodone Crushed HFHC")

Each treatment with OxyContin and IR oxycodone consisted of 40 mg of oxycodone hydrochloride (HCl). Each treatment with Oxycodone DETERx consisted of 36 mg of oxycodone base, which is equivalent to 40 mg of oxycodone HCl.

Prior to study drug administration, subjects fasted for at least 10 hours, then were served a standardized, HFHC breakfast; this meal started 30 minutes prior to the scheduled administration of study drug and was to be consumed in its entirety within 20 minutes (i.e., by at least 10 minutes prior to dosing). The HFHC meal followed the recommendation described in the Guidance for Industry: Food Effect Bioavailability and Fed Bioequivalence Studies, dated December 2002.[1]

For each Treatment Period, subjects were admitted to the clinic the day before study drug administration and received 50 mg of naltrexone approximately 13 hours prior to and 1 hour prior to study drug administration. For Oxycodone DETERx and OxyContin Treatment Periods (intact and crushed), blood samples for oxycodone concentration analysis were collected pre-dose and at scheduled time points until 36 hours post-dose. For the IR oxycodone Treatment Period (crushed), blood samples for oxycodone concentration analysis were collected pre-dose and at scheduled times until 24 hours post-dose. Subjects were confined to the clinic until the last PK sample in each Treatment Period had been collected.

A washout of at least 5 days was observed between dosing with study drug in each Treatment Period. Based on a 5-day washout, subjects checked in to the clinic on the evenings of Days -1, 5, 10, 15 and 20 were dosed on the mornings of Days 1, 6, 11, 16 and 21. Actual dates could vary if longer washout intervals were observed between any Periods.

Appropriate equipment and therapeutic agents for Advanced Cardiac Life Support were immediately available for 12 hours after study drug administration in each Treatment Period. Prior to study drug administration, study site personnel ensured that all equipment had been maintained according to manufacturer's specifications and that resuscitation drugs had not reached their expiration date. At least one member of the study site staff was certified in Advanced Cardiac Life Support and was present for 12 hours after study drug administration in each Treatment Period.

Xtampza (Oxycodone DETERx) 40 mg crushed was prepared at the clinical site according to a crushing procedure established in Category 1 in vitro formulation manipulation studies, selected from among a number of methods as the method that has the largest effect on particle size reduction (PSR) and increase in dissolution rate of the various in vitro PSR techniques attempted as follows:

- A 4.5-inch ceramic mortar and a pestle were used to crush study drug.

• The contents of a single, 40-mg Oxycodone DETERx capsule were crushed by grinding using a circular motion (approximately 100 revolutions per minute, equivalent to approximately 1 and a half revolutions per second) for 2 minutes (using a digital timer).

• After grinding was complete, a spatula was used to remove any crushed microspheres that were stuck to the pestle by scraping the surface of the pestle; the mortar was used to catch any dislodged study drug. The crushed contents in the mortar were then transferred onto a 6 inch by 6 inch weighing paper using a spatula and then into a dosing cup, taking care to minimize any sample losses.

• The contents of the dosing cup were administered to the subject followed by consumption of 240 mL of water; study staff performed a visual oral cavity check to ensure all study drug had been consumed.

Crushed Xtampza (Oxycodone DETERx) microspheres were transferred dry to the subject, who consumed water after swallowing the crushed microspheres.

Crushed OxyContin OP was prepared as follows:

- Place a large sheet of butcher or construction paper on the pharmacy bench. Crease a sheet of weigh paper in half diagonally, and place on top of large paper surface. Place (b) (4)® ®fine grater on top of weigh paper.
- Using needle nose pliers, apply a firm grip to the OxyContin OP tablet.
- Run tablet over grating surface. When grating, contact (b) (4) surface in only 1 direction, ie, against the serrated protrusions in the (b) (4) surface.
- Continue grating, adjusting the tablet as necessary in the needle nose pliers, until all material passes through the (b) (4) e surface.
- Brush all surfaces of the pliers and (b) (4) with a pastry brush so that all visible powder collects on the weigh paper. A (b) (4) may be used to reduce the effect of static charge on transfer of powder.
- Transfer material from the weigh paper into the medicinal cup or glass scintillation vial. Use of a (b) (4) was permitted to reduce the effect of static charge on transfer of powder.
- Transfer any powder on the large butcher or construction paper onto the weigh paper and subsequently into the medicinal cup or glass scintillation vial, again, using the (b) (4) if needed.
- Change to a fresh (b) (4) after crushing 6 tablets using the method described in Steps 1-7.

Investigational Product

Test (T): Oxycodone DETERx 36 mg capsule (i.e., 36 mg of oxycodone base, equivalent to 40 mg oxycodone HCl) (Xtampza™ ER, manufactured by Patheon, Inc. [Cincinnati, OH USA]) for Collegium Pharmaceutical, Inc. (Canton, MA USA). Batch number: 3141993; Expiry date: 31 December 2017

Reference Drugs

Reference 1 (R1): OxyContin 40 mg oxycodone HCl tablet (Purdue Pharma L.P., Stamford, CT USA). Batch number: W1PS1; Expiry date: August 2018

Reference 2 (R2): IR oxycodone 20 mg (2 x 20 mg per dose) oxycodone HCl tablet (b) (4) Batch number: 13020A; Expiry date: November 2019

Adjunctive Drug

Naltrexone 50 mg tablet manufactured by (b) (4)
Batch number: 1170Y94899; Expiry date: October 2020

Study Drug Treatments

Subjects completing the study received each of the 5 treatments shown in Table S-1, below. Treatment sequence was randomized according to a 5 x 5 Williams square design prepared prior to the start of the study, assigning 4 - 5 subjects to each sequence. Study drug treatments were as follows:

Table S-1 Study Drug Treatments

Treatment	Treatment Description	Study Drug	Dose and Form of Administration
A	Test, Intact	Oxycodone DETERx	1 x 36 mg capsule (equivalent to 40 mg oxycodone HCl), intact
B	Test, Crushed	Oxycodone DETERx	1 x 36 mg capsule (equivalent to 40 mg oxycodone HCl), microspheres crushed
C	Reference 1, Intact	OxyContin	1 x 40 mg tablet intact
D	Reference 1, Crushed	OxyContin	1 x 40 mg tablet crushed
E	Reference 2, Crushed	IR oxycodone	2 x 20 mg tablets crushed

HCl=hydrochloride; IR=immediate-release

Analysis Populations

The Safety Population consisted of all subjects who received at least one dose of study drug and for whom there was at least one post-treatment safety observation (e.g., treatment emergent adverse event [TEAE], vital signs measurement, oxygen saturation, hematologic, biochemical and urinalysis laboratory parameters, or physical examination).

The PK Population consisted of all subjects who completed at least 2 of the 5 Treatment Periods, had data sufficient for the determination of PK parameters, did not experience emesis within 12 hours of study drug administration, and did not have a protocol deviation that could have compromised the integrity of PK results.

Pharmacokinetic Assessment

For Oxycodone DETERx and OxyContin Treatment Periods (intact and crushed), serial blood samples for measurement of plasma concentrations of oxycodone were collected prior to study drug administration and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 7.0, 8.0, 9.0, 10.0, 12.0, 24.0 and 36.0 hours post-dose.

For the IR oxycodone Treatment Period (crushed), serial blood samples for measurement of plasma concentrations of oxycodone were collected prior to study drug administration and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 8.0, 12.0, 16.0 and 24.0 hours post-dose.

Pharmacokinetic Endpoints

Oxycodone PK parameters were calculated using standard noncompartmental analysis (NCA) methods.

Table S-2 Pharmacokinetic Parameters

Parameter	Definition
C_{max}	Maximum observed plasma concentration
T_{max}	Time to reach maximum plasma concentration
T_{lag}	Absorption lag time
$AUC_{(0-t)}$	Area under the plasma concentration-time curve from 0 to final time with a concentration ≥ validated lower limit of the bioanalytical method(s) (LOQ)
$AUC_{(inf)}$	Area under the plasma concentration-time curve to infinity
$AUC_{\%extrap}$	Percentage of $AUC_{(inf)}$ that is due to extrapolation from C_{last} to infinity (where C_{last} is the last measurable concentration)
AQ	Abuse quotient (C_{max}/T_{max})
PAUC	Partial area under the plasma concentration-time curve from 0 to all blood sampling time points
$PAUC_{(0-5)}$	Partial area under the plasma concentration-time curve from 0 to the 5-hour sampling time point
Parameter	**Definition**
λz	Terminal elimination rate constant
$t_{1/2}$	Terminal elimination half-life
CL/F	Apparent Clearance = $Dose/AUC_{(inf)}$
Vz/F	Volume of distribution uncorrected for bioavailability
Fr	Relative bioavailability = $AUC_{(inf)}$ (test product)/$AUC_{(inf)}$ (reference product) * 100 (where the reference is IR oxycodone crushed)

Protocol Amendments:

The original protocol, dated 21 December 2015, was not amended. A copy of the protocol is provided in Appendix 16.1.1.

Reference ID: 4161285

Criteria for Inclusion:

1. Subject provided written informed consent prior to participation in the study.
2. Subject had the ability to read and/or follow written and oral instructions.
3. Subject was male or female 18-50 years of age (inclusive) at the time of consent.
4. Subject did not have any dietary restrictions or food allergies, was able to fast for at least 10 hours and was able to consume the complete, assigned HFHC meal within the allotted time prior to study drug administration.
5. Female subjects had a negative serum pregnancy test at Visit 1 and a negative urine pregnancy test at admission for each Treatment Period.
6. Female subjects of childbearing potential were willing to use an acceptable method of birth control throughout the study. Acceptable birth control methods included:
    - Total abstinence from heterosexual intercourse for a minimum of 1 complete menstrual cycle prior to Visit 1;
    - A vasectomized partner that had a vasectomy a minimum of 6 months prior to Visit 1;
    - Use of contraceptives* (oral, parenteral or transdermal) for a minimum of 12 weeks prior to the start of study drug administration in Treatment Period 1;
    - Use of an intrauterine device for a minimum of 12 weeks prior to the start of study drug administration in Treatment Period 1; or
    - Use of a dual method including condoms, sponges, diaphragms, or vaginal rings with spermicidal jellies, films, foams, creams or suppositories throughout the study.

    * Subjects taking birth control pills must have taken the same type pill for at least 12 weeks prior to the Visit 1 and were willing not to change their type of pill and dosing regimen during the study. Subjects who discontinued the use of birth control pills must have discontinued usage at least 8 weeks prior to the start of study drug administration in Treatment Period 1.

    Subjects considered not of childbearing potential must have been surgically sterile (total hysterectomy, bilateral salpingo-oophorectomy or tubal ligation) for greater than one year post-menopausal, defined as a complete cessation of menstruation for at least one year.
7. Subject was in general good health based on screening physical examination, vital signs, medical history, 12-lead electrocardiogram (ECG) and clinical laboratory values (hematology, serum chemistry and urinalysis).
8. Subject had a negative urine drug screen, saliva alcohol test and urine cotinine test at Visit 1 and at admission for each Treatment Period.

Reference ID: 4161285

Exclusion Criteria

1. Female subject who was pregnant, planning a pregnancy or breastfeeding.
2. Subject had a Body Mass Index (BMI) > 33 kg/m^2.
3. Subject had any clinically significant unstable medical abnormality or chronic disease of the cardiovascular, gastrointestinal, respiratory (e.g., chronic obstructive pulmonary disease), hepatic or renal systems.
4. Subject had any clinically significant deviation from normal in physical examination, vital signs, 12-lead ECG or clinical laboratory measurements, as determined by the Investigator.
5. Subject had history of alcohol and/or drug abuse.
6. Subject could not refrain from taking medications (prescription, over-the-counter [OTC], or behind-the-counter), supplements, nutraceuticals or herbs for 24 hours prior to admission to the clinic for Treatment Period 1 and for the duration of the study except those allowed by protocol.
7. Subject who could not refrain from using caffeine or caffeine containing products or alcohol within 24 hours prior to each admission to the clinic. Heavy caffeine users who could not tolerate stopping caffeine without symptoms were excluded.
8. Subject currently used tobacco products or smoked cigarettes. Subject must have stopped using tobacco products or smoking cigarettes ≥ 30 days prior to Visit 1 and must have been willing to refrain from tobacco products or smoking cigarettes for the duration of the study.
9. Subjects could not consume grapefruit, pomegranate, pomelo and star fruit juice/products, as well as foods containing poppy seeds, Seville oranges and/or drinks or foods containing quinine (i.e., tonic water) within 7 days prior to the start of study drug administration in Treatment Period 1 and/or was unwilling to abstain from these products for the duration of the study.
10. Subjects were not willing to refrain from strenuous activity for 3 days prior to admission to the clinic for Treatment Period 1 and for the duration of the study.
11. Subject had a disorder or history of a condition (e.g., malabsorption, gastrointestinal surgery) that may have interfered with drug absorption, distribution, metabolism or excretion.
12. Subject was known to be allergic or hypersensitive to any of the ingredients in the study drug.
13. Subject had participated in any investigational study within 30 days prior to Visit 1 or was currently participating in another clinical study.
14. Subject had experienced significant blood loss within 60 days or had donated plasma within 72 hours prior to the start of study drug administration in Treatment Period 1.
15. Subject had an intolerance to or difficulty with venipuncture or catheter insertion for blood sampling.
16. Subject tested positive at Visit 1 for HIV or was known to be seropositive for HIV.
17. Subject tested positive at Visit 1 for hepatitis B surface antigen or hepatitis C antibody, or had a history of a positive result.
18. Subject was previously enrolled in Study CP-OXYDET-25.
19. Subject was a staff member or relative of a staff member.
20. Subject was not able to meet the study attendance requirements.

Reference ID: 4161285

Duration of Treatment:

Following Visit 1 that was to be conducted no more than 14 days and no fewer than 2 days prior to the first dose of study drug, subjects returned to the study center for 5 inpatient treatment visits, each of which included 2 nights of confinement to the study center. A minimum 5-day washout was maintained between study drug administrations. Assuming 5-day washouts between all Treatment Periods, the maximum duration of participation was 35 days and the minimum participation was 23 days. See Table 9-3, Schedule of Assessments for details.

Determination of Sample Size

The study planned to enroll approximately 42 subjects to ensure the completion of 36 evaluable subjects. A population of 36 evaluable subjects would provide 80% power to detect an equivalence ratio between 0.8 and 1.25 if the true mean ratio was 1.10 or less and the coefficient of variation was 21% or less.

Analysis Methods:

Pharmacokinetic Analysis

The plasma oxycodone PK parameters shown in Table S-2 were calculated using NCA methods.

T_{max} was analyzed using nonparametric analysis without transformation. The 25% Quantile (Q1), 50% Quantile (Median), and 75% Quantile (Q3) were calculated from the Walsh Averages of the treatment differences. Wilcoxon Signed Rank Test was used to compare the Test treatments versus the Reference treatment. T_{max} was not transformed and results are reported.

Plots are presented for the mean (± standard deviation [SD]) plasma concentration versus time, and for individual subject plasma concentration data versus time on linear and semi-logarithmic axes.

Bioequivalence Analysis

Primary oxycodone PK parameters C_{max}, $AUC_{(0\text{-}t)}$ and $AUC_{(inf)}$ were compared among treatments using an Analysis of Variance (ANOVA) statistical model with sequence, treatment and period as the fixed effects and subject within sequence as a random effect, using the natural logarithms of the data. Analysis was performed using the SAS® (SAS Institute, Inc., Carey, NC) PROC GLM procedure.

Confidence intervals (90% [CI]) were constructed for the least squares geometric mean ratios (LSGMR, GMR) of all 3 parameters for selected treatment comparisons using the natural log transformed data and the 2 one-sided t-tests procedure. The GMR and associated 90% CI were exponentiated back to the original scale. Bioequivalence (BE) was concluded if the 90% CI of the GMR for a specific comparison fell entirely within the range of 80.0% to 125.00%, inclusive.

The primary BE analyses compared the following treatment pairs:

- B vs. E (Oxycodone DETERx Crushed HFHC vs. IR Oxycodone Crushed HFHC)
- D vs. E (OxyContin Crushed HFHC vs. IR Oxycodone Crushed HFHC)

Secondary BE analyses compared these additional treatment pairs:

- B vs. A (Oxycodone DETERx Crushed HFHC vs. Oxycodone DETERx Intact HFHC)
- D vs. C (OxyContin Crushed HFHC vs. OxyContin Intact HFHC)
- A vs. E (Oxycodone DETERx Intact HFHC vs. IR Oxycodone Crushed HFHC)
- C vs. E (OxyContin Intact HFHC vs. IR Oxycodone Crushed HFHC)
- A vs. C (Oxycodone DETERx Intact HFHC vs. OxyContin Intact HFHC)
- B vs. D (Oxycodone DETERx Crushed HFHC vs. OxyContin Crushed HFHC)

Reference ID: 4161285

RESULTS:

A total of 42 healthy subjects (31 male, 11 female) between the ages of 18 and 46 were enrolled and randomized to treatment: all 42 subjects (100%) were included in the Safety Population; 35 subjects (83.3%) completed the study and received all planned doses of study drug; 7 subjects (16.7%) discontinued prematurely; 3 subjects (7.1%) discontinued due to an AE, 3 subjects (7.1%) withdrew consent and 1 subject (2.4%) demonstrated significant non-compliance with the requirements of the study.

The PK Population included the following number of subjects for each treatment:

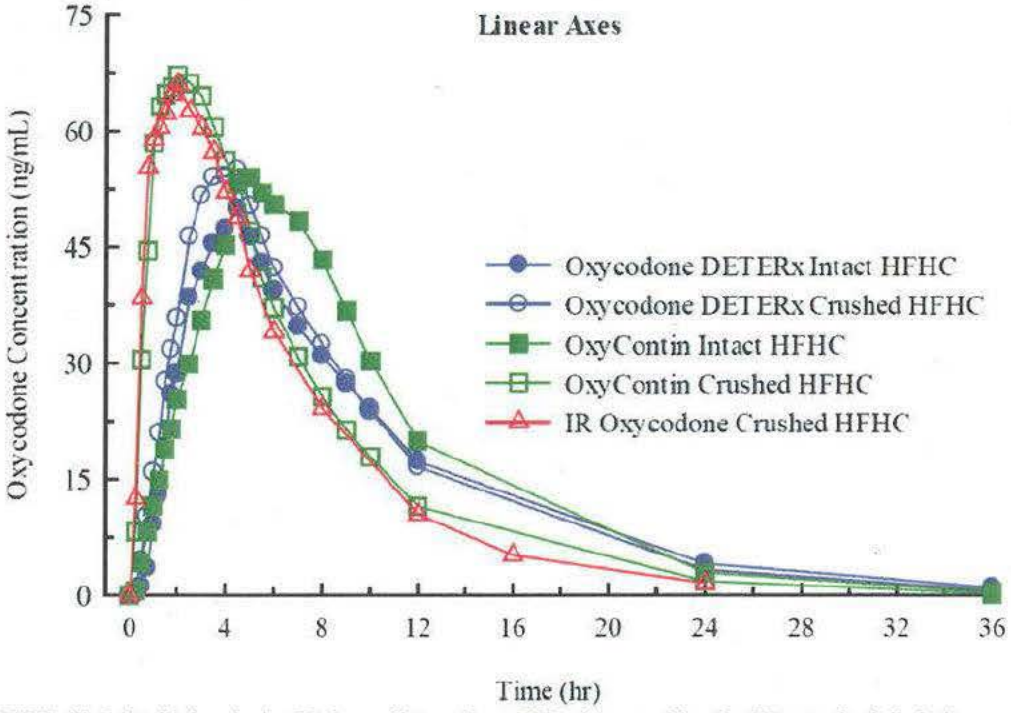
- Treatment A: 38 subjects (90.5%)
- Treatment B: 39 subjects (92.9%)
- Treatment C: 38 subjects (90.5%)
- Treatment D: 39 subjects (92.9%)
- Treatment E: 37 subjects (88.1%)

Demographics: Subjects were representative of a healthy adult male and female population, ranging from 18 to 46 years of age. Overall mean (SD) age was 30.5 (0.95) years and mean (SD) BMI was 26.71 (0.538) kg/m^2. Racial composition was 20 (47.6%) Black or African-American and 22 (52.4%) White.

Pharmacokinetic Results

Plasma oxycodone concentration-time profiles are shown by treatment on a linear scale in Figure S-1, below.

Figure S-1 Mean (SD) Plasma Oxycodone Concentration vs. Time by Treatment – PK Population



HFHC=high-fat, high-calorie; IR=immediate-release; PK=pharmacokinetic; SD=standard deviation

Source: Appendix 16.6.1, Figure 3

Conclusions:

The primary objective of this study was to assess the safety and PK of Xtampza or Oxycodone DETERx intact and crushed relative to OxyContin (Oxycodone extended-release tablets) intact and crushed and an IR formulation of oxycodone crushed.

The results of this study showed the following:

- Administration of Oxycodone DETERx Crushed HFHC did not lead to any change in the PK profile compared with Oxycodone DETERx Intact HFHC. Exposure, as measured by C_{max} and AUC, was bioequivalent between the two treatments. Compared with administration of IR Oxycodone Crushed HFHC, administration of Oxycodone DETERx Crushed HFHC or Oxycodone DETERx Intact HFHC resulted in a significantly lower mean C_{max} at a later median T_{max}, but equivalent AUC.
- Administration of OxyContin (Oxycodone extended-release tablets) Crushed HFHC resulted in an increase in C_{max} and decrease in T_{max} compared with OxyContin (Oxycodone extended-release tablets) Intact HFHC and a concentration-time profile, mean C_{max}, and median T_{max} that were comparable to those from IR Oxycodone Crushed HFHC. Compared with administration of IR Oxycodone Crushed HFHC, administration of OxyContin (Oxycodone extended-release tablets) Crushed HFHC resulted in BE for C_{max}, AUC(0-t), and AUC(inf).
- Oxycodone DETERx Intact HFHC and OxyContin(Oxycodone extended-release tablets) Intact HFHC were bioequivalent with respect to C_{max}, AUC(0-t), and AUC(inf).
- Administration of OxyContin (Oxycodone extended-release tablets) Crushed HFHC resulted in an increase in C_{max} and a decrease in T_{max} compared with Oxycodone DETERx Crushed HFHC. Compared with administration of Oxycodone DETERx Crushed HFHC, administration of OxyContin (Oxycodone extended-release tablets) Crushed HFHC resulted in a C_{max} that was significantly higher, but bioequivalent for AUC(0-t) and AUC (inf).

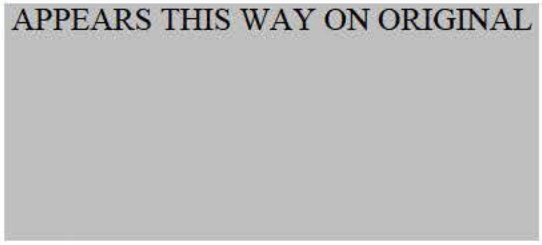
3.2.2 Synopsis of Study CP-OXYDET-28:

Name of Company: Collegium Pharmaceutical, Inc.	**Individual Study Table Referring to Part of the Dossier**	(For National Authority Use only)
Name of Finished Product: Oxycodone DETERx	**Volume:**	
Name of Active Ingredient: Oxycodone	**Page:**	
Title of Study: Assessment of the Oral Human Abuse Liability and Pharmacokinetics of Oxycodone DETERx®		
Investigator and Study Center: This study was conducted at a single site in the United States of America (USA): Debra J. Kelsh MD. Vince and Associates Clinical Research, Overland Park, Kansas.		
Publication (reference): None		
Study Start Date: 18Mar2016 (date of first screening) **Study Completion Date**: 12Dec2016 (date of last contact)	**Phase of Development:** 1	
Objective: The primary objective of this study was to evaluate the abuse liability and pharmacokinetics (PK) of oxycodone after intact and chewed oral administration of Oxycodone DETERx under fed (high-fat, high-calorie [HFHC]) and fasted conditions, and crushed immediate-release (IR) oxycodone under fasted conditions.		
Methodology: This was a randomized, double-blind, triple-dummy, active- and placebo-controlled, single-dose, 6-treatment, 6-period crossover comparison study designed to evaluate the oral abuse liability and PK of oxycodone after intact and chewed oral administration of Oxycodone DETERx under fed (HFHC) and fasted conditions, compared with crushed IR oxycodone in solution under fasted conditions. Subjects who successfully completed the Screening Phase (Visit 1) returned to the clinical research unit as inpatients to complete the Drug Discrimination Phase. The Drug Discrimination Phase comprised a Naloxone Challenge Test to confirm that subjects were not opioid tolerant and a Drug Discrimination Test to ensure that subjects could differentiate between the effects of a single 40 mg dose of crushed IR oxycodone dosed per os (PO) in solution and placebo powder in solution. Subjects who successfully completed the Naloxone Challenge Test remained as inpatients to complete the Drug Discrimination Test. In a 2-way crossover, 1:1 ratio, double-blind, randomized design, subjects received a single PO dose of the following treatments under fasted conditions:		

Reference ID: 4161285

Oxycodone DETERx 40 mg chewed was administered as follows:

- A single, 40-mg Oxycodone DETERx capsule was opened and the contents poured into a dosing cup.
- Subjects were instructed to take the study drug and chew the capsule contents for 2 minutes prior to swallowing.
- After chewing the study drug for 2 minutes, 120 mL of water was used by the subject to rinse his/her oral cavity; the water was swallowed.
- Study staff then performed a visual oral cavity check to ensure that study drug microspheres had not accumulated/deposited at the tooth-gum interface.
- The subject then rinsed and swallowed the remaining 120 mL of water after which another visual inspection of the oral cavity was conducted to ensure consumption of all of the study drug microspheres.



- Crushed IR oxycodone 40 mg. in solution
- Placebo powder. in solution

Each dose was separated by at least 24 hours. Subjects were discharged from the clinical research unit approximately 24 hours after the second dose. if deemed safe by the Investigator. Subjects who were eligible to continue participating in the study returned to the clinical research unit to begin the Double-blind Treatment Phase. A period of 5 to 21 days separated the second treatment in the Drug Discrimination Test and the first treatment in the Double-blind Treatment Phase.

During the Double-blind Treatment Phase, subjects were randomized in a 1:1:1:1:1:1 ratio to receive a single dose of 6 treatments in a double-blind, triple-dummy crossover manner (1 per Treatment Period):

Treatment	Chewed	Intact Capsule	IR Solution	Fed/Fasted
A	DETERx placebo	**Oxycodone DETERx**	Placebo	HFHC
B	DETERx placebo	**Oxycodone DETERx**	Placebo	Fasted
C	**Oxycodone DETERx**	DETERx placebo	Placebo	HFHC
D	**Oxycodone DETERx**	DETERx placebo	Placebo	Fasted
E	DETERx placebo	DETERx placebo	**IR oxycodone**	Fasted
F	DETERx placebo	DETERx placebo	Placebo	HFHC

HFHC=high-fat, high-calorie; IR=immediate-release. Active treatments (each dose equivalent to 40 mg of oxycodone hydrochloride) are in bold.

Serial pharmacodynamic (PD) assessments and PK sampling were conducted up to 36 hours after each study drug administration. Safety monitoring included recording of adverse events (AEs) and concomitant medications: 12-lead electrocardiogram (ECG) at Screening; clinical laboratory assessments (chemistry, hematology, urinalysis) at Screening and end of study; and regular assessments of vital signs measurements (including oxygen saturation), urine drug screen (UDS), breath alcohol testing, pregnancy testing, and physical examination findings.

For all Treatment Periods, subjects remained in the clinic until approximately 36 hours after dosing. Subjects were only discharged if the Investigator deemed it was safe; subjects could be asked to reside in the clinical research unit for a longer period of time, if necessary. Each treatment was separated by a period of 5 to 21 days.

Subjects who enrolled into the Double-blind Treatment Phase were to be contacted via phone approximately 5 (± 2) days following discharge from the Double-blind Treatment Phase or after early discontinuation from the study for a Safety Follow-up Visit.

Number of Subjects (Planned and Analyzed):

Planned: Forty-eight completed subjects were planned for this study. A sample size of 48 completed subjects was estimated to provide at least 90% power to detect treatment differences of ≥ 9.0 points in maximum effect (E_{max}) for the bipolar Drug Liking visual analog scale (VAS), at the 1-sided significance level of 0.025, and estimated $\delta_1 = 3.5$, using a paired means test and correlation of 0.5, and assuming standard deviation differences of 11.0 points.

Analyzed: A total of 174 subjects entered the Drug Discrimination Phase, passed the Naloxone Challenge Test, and received at least one study drug dose in the Drug Discrimination Test; these subjects comprised the Drug Discrimination Safety Population. A total of 75 subjects passed the Drug Discrimination Test and entered the Double-blind Treatment Phase. The 75 subjects who entered the Double-blind Treatment Phase represent the Safety Population, of which 71 subjects had sufficient PK data and represent the PK Population. A total of 52 subjects completed the study and comprise the PD Population.

Reference ID: 4161285

Diagnosis and Main Criteria for Inclusion:

Healthy, adult male and female subjects, between 18 and 55 years of age, inclusive, who were nondependent recreational opioid users, defined as users of opioids for non-medical purposes (i.e., for psychoactive effects) on at least 10 occasions within the last year and at least once in the 12 weeks prior to Screening (Visit 1).

Test Product, Dose, and Mode of Administration:

During the Double-blind Treatment Phase, Oxycodone DETERx 36 mg (Xtampza® ER; equivalent to 40 mg of oxycodone hydrochloride [HCl]) was administered orally (intact or chewed) under fasted and fed conditions. Oxycodone DETERx capsules were supplied in bottles of 100 by Collegium Pharmaceutical, Inc. (Canton, MA; Batch No. 3141993, Expiry/Retest Date: Dec2017).

Reference Therapy, Dose, and Mode of Administration:

Naloxone Challenge Test:

An initial dose of naloxone HCl 0.2 mg was administered by intravenous (IV) bolus followed by an additional 0.6 mg of IV naloxone if no evidence of withdrawal occurred within 1 minute as assessed by the Clinical Opiate Withdrawal Scale (COWS). Naloxone HCl Injection, USP (0.4 mg/mL multiple-use [10 mL] vials) was obtained by the study site from (b) (4) Multiple lots of Naloxone HCl were utilized; refer to Appendix 16.1.6 for a full list of lots and expiration dates.

Drug Discrimination Test:

For IR oxycodone 40 mg, 2 oxycodone HCl 20 mg tablets were crushed and dissolved in 50 mL solution and administered orally. Oxycodone HCl 20 mg tablets were obtained by the site from (b) (4), Lot No. 13021B, Expiry Date: 30Nov2019).

Microcrystalline cellulose (placebo powder in 50 mL solution, oral) was procured by the study site from (b) (4) Lot No. 14A29-U12-017294, Expiry Date: 30Nov2016 used for subjects dosed through 28Nov2016) and (b) (4) Lot No. 2EE0206, Expiry Date: 27Aug2018 for subjects dosed after 28Nov2016).

Denatonium Benzoate (taste masking agent dissolved in 1 part-per-million solution) was procured by the study site from (b) (4), Lot No. 2EH0269, Expiry Date: 31Jul2019).

Double-blind Treatment Phase:

For IR oxycodone 40 mg, 2 oxycodone HCl 20 mg tablets were crushed and dissolved in 50 mL solution and administered orally. Oxycodone HCl 20 mg tablets were obtained by the site from (b) (4), Lot No. 13021B, Expiry Date: 30Nov2019).

Placebo DETERx capsules were administered orally (intact or chewed) under fasted and fed conditions. Placebo DETERx capsules were supplied by the Sponsor and shipped to the study site by Collegium Pharmaceutical, Inc. (Canton, MA; in blister packaging, Lot No. 76147047, Expiry Date: May2017).

Microcrystalline cellulose (placebo powder in 50 mL solution, oral) was procured by the study site from (b) (4) Lot No. 14A29-U12-017294, Expiry Date: 30Nov2016 used for subjects dosed through 28Nov2016) and (b) (4) Lot No. 2EE0206, Expiry Date: 27Aug2018 for subjects dosed after 28Nov2016).

Denatonium Benzoate (taste masking agent dissolved in 1 part-per-million solution) was procured by the study site from (b) (4), Lot No. 2EH0269, Expiry Date: 31JJul2019).

Reference ID: 4161285

Criteria for Evaluation:

Pharmacodynamic Assessments: Serial PD assessments were collected at pre-dose (as applicable) and at multiple time points post-dose. Subjective assessments included Drug Effects Questionnaire (DEQ) drug liking, feeling high, any drug effects, good effects, bad effects, feel sick, nausea, sleepy, and dizzy; Overall (Global) Drug Liking; Addiction Research Center Inventory-Morphine Benzedrine Group (ARCI/MBG); Take Drug Again Assessment; and Price Value Assessment Questionnaire (PVAQ). Pupil diameter (pupillometry) was included as an objective assessment.

The following PD endpoints were derived: E_{max} from 0 to 24 hours post-dose (also derived from 0 to 8 hours post-dose for Drug Liking); time to maximum (peak) effect (TE_{max}); minimum (peak) effect (E_{min}) for bipolar scales only; time to minimum (peak) effect (TE_{min}) for bipolar scales only; area under the effect curve (AUE) to 1 hour (AUE_{0-1h}), AUE_{0-2h}, AUE_{0-4h}, AUE_{0-8h}, and AUE_{0-24h}, as applicable. For Overall (Global) Drug Liking and the Take Drug Again Assessment, the E_{max} and mean response (E_{mean}) averaging the 8- and 24-hour assessments were calculated.

Pharmacokinetic Assessments: Serial blood samples to measure plasma oxycodone concentrations were collected at pre-dose and at multiple time points post-dose.

The following PK endpoints were derived for oxycodone using noncompartmental PK methods: maximum plasma concentration (C_{max}), time of C_{max} (T_{max}), absorption lag time (T_{lag}), area under the plasma concentration-time curve (AUC) from zero to final time with a concentration ≥ validated lower limit of quantitation ($AUC_{(0-t)}$), AUC to infinity ($AUC_{(inf)}$), percentage of $AUC_{(inf)}$ that is due to extrapolate from the last measurable plasma concentration to infinity ($\%AUC_{extrap}$), partial AUC (PAUC), abuse quotient (AQ: C_{max}/T_{max}), terminal elimination rate constant (λ_z), terminal elimination half-life ($t_{½}$), total clearance uncorrected for bioavailability (CL/F), volume of distribution uncorrected for bioavailability (V_z/F), and relative bioavailability (Fr).

Safety Assessments: Safety was evaluated based on treatment-emergent adverse events (TEAEs), clinical laboratory assessments, vital signs (including oxygen saturation), 12-lead electrocardiogram (ECG), urine drug screen (UDS), breath alcohol testing, pregnancy testing, and physical examinations.

Statistical Methods:

Analysis Populations:

Pharmacodynamic Population: Subjects who completed all 6 Treatment Periods with at least 1 PD assessment in each Treatment Period. This was the primary population for PD analyses.

Pharmacokinetic Population: Subjects who completed at least 2 active Treatment Periods, who had sufficient quantifiable plasma concentration data to provide C_{max} and AUC data, and who did not experience vomiting within 12 hours of dosing for Oxycodone DETERx, or within 2 x median T_{max} (2 x 1.07 = 2.14 hours) of dosing for IR oxycodone.

Drug Discrimination Safety Population: All subjects who received at least 1 dose of study drug during the Drug Discrimination Phase and for whom there was at least 1 post-dose safety observation.

Safety Population: All subjects randomized into the Double-blind Treatment Phase who received at least 1 dose of study drug during the Double-blind Treatment Phase and for whom there was at least 1 post-dose safety observation in this phase.

Reference ID: 4161285

Pharmacodynamic Analyses: All PD endpoints were analyzed using a linear mixed model with fixed effects for sequence, period, and treatment, and a random effect for subject nested in sequence. Least-squares (LS) means along with 95% confidence intervals (CIs) were provided for each treatment. Least-squares mean differences along with 95% CIs were provided for all pairwise treatment comparisons between treatments. The distribution of the residuals from each parametric model was examined to determine whether substantial departures from normality were apparent using the Shapiro Wilk test (tested at $\alpha = 0.01$). If the residuals were not normally distributed, a non-parametric analysis (the same procedure after ranked transformation) was to be provided in addition to the parametric analysis.

The primary analysis was based on the pairwise comparison between chewed Oxycodone DETERx and crushed IR oxycodone fasted for Drug Liking E_{max} with the following hypothesis:

$$H_o: \mu_C - \mu_T \leq (\mu_C - 50)\delta^* \quad versus \quad H_a: \mu_C - \mu_T > (\mu_C - 50)\delta^*$$

where $0.1 < \delta^* < 1$. $(\mu_c\text{-}50)\ \delta^*$ was defined as δ_1. μ_C is the mean of the control treatment, crushed IR oxycodone 40 mg in solution fasted (Treatment E), and μ_T is the mean of the test treatment, chewed Oxycodone DETERx fasted (Treatment D) or chewed Oxycodone DETERx HFHC (Treatment C). A δ^* of 0.1 was used in the primary statistical analysis and if the test results were statistically significant, then the δ^* value was incremented by 0.05 until a statistically non-significant result was obtained for the primary statistical analyses. The last δ^* prior to non-

significance was identified and footnoted in the summary table of the analyses for the DEQ Drug Liking outcome measure.

Additionally, the hypothesis for the validation test for Drug Liking E_{max} between IR oxycodone and placebo treatment was:

$$H_o: \mu_C - \mu_P \leq \delta_2 \quad versus \quad H_a: \mu_C - \mu_P > \delta_2$$

where $\delta_2 = 15$.

For PD statistical analyses, significance for the primary comparisons was declared if the lower 95% CI was greater than δ_1. Significance for the validation test was declared if the lower 95% confidence interval was greater than δ_2. Significance testing for all other endpoints and comparisons was 2-tailed using $\alpha = 0.05$, unless otherwise specified.

The following treatment comparisons were made for each of the PD endpoints:

- Treatment E (crushed IR oxycodone fasted) versus Treatment F (placebo HFHC: Validity):
- Treatment E (crushed IR oxycodone fasted) versus Treatment D (chewed Oxycodone DETERx fasted: Primary Comparison):
- Treatment E (crushed IR oxycodone fasted) versus Treatment C (chewed Oxycodone DETERx HFHC: Primary comparison):
- Treatment C (chewed Oxycodone DETERx HFHC) versus Treatment A (intact Oxycodone DETERx HFHC: Secondary comparison):
- Treatment D (chewed Oxycodone DETERx fasted) versus Treatment A (intact Oxycodone DETERx HFHC: Secondary comparison):
- Treatment D (chewed Oxycodone DETERx fasted) versus Treatment B (intact Oxycodone DETERx fasted: Secondary comparison):
- Treatment E (crushed IR oxycodone fasted) versus Treatment A (intact Oxycodone DETERx HFHC):
- Treatment E (crushed IR oxycodone fasted) versus Treatment B (intact Oxycodone DETERx fasted):
- Treatment A (intact Oxycodone DETERx HFHC) versus Treatment F (placebo HFHC):
- Treatment B (intact Oxycodone DETERx fasted) versus Treatment F (placebo HFHC):
- Treatment C (chewed Oxycodone DETERx HFHC) versus Treatment F (placebo HFHC):
- Treatment D (chewed Oxycodone DETERx fasted) versus Treatment F (placebo HFHC).

A responder analysis was conducted using Drug Liking E_{max}. Percent reduction in Drug Liking E_{max} was used to define a responder at several cutoffs. A responder was defined as a subject who had at least a prespecified level of reduction, where levels from 10% to 90% in 10% increments

Reference ID: 4161285

were presented in an exploratory fashion. The number and percent of subjects determined as responders and non-responders were presented. A contingency table of the percent reduction of Drug Liking E_{max} for chewed and intact Oxycodone DETERx relative to crushed IR oxycodone fasted versus the Drug Liking E_{max} for crushed IR oxycodone fasted were presented. The 10% categories were used for the percent reduction and IR oxycodone E_{max} were split into categories incremented by 5 (i.e., ≤55, (55-60], (60-65], (65-70], up to (95-100]).

Pharmacokinetic Analyses: All PK parameters were calculated using non-compartmental analysis. The PK parameters for oxycodone — C_{max}, $AUC_{(0-t)}$, and $AUC_{(inf)}$ — were compared among treatments using an analysis of variance (ANOVA) statistical model with sequence, treatment, and period as the fixed effects and subject within sequence as a random effect, using the natural logarithms of the data. Confidence intervals (90% CI) were constructed for the LS geometric mean ratios (LSGMR) of all 3 parameters for the treatments being compared using the natural log-transformed data and the two 1-sided t-tests procedure. The LSGMRs and associated 90% CI were exponentiated back to the original scale. Bioequivalence (BE) was to be concluded if the 90% CIs of the LSGMRs for a specific comparison fell entirely within 80.0% to 125.00%. The following treatment comparisons were made for ln-transformed $AUC_{(0-t)}$, $AUC_{(inf)}$, and C_{max}:

- Treatment A (intact Oxycodone DETERx HFHC) versus Treatment E (crushed IR oxycodone fasted);
- Treatment B (intact Oxycodone DETERx fasted) versus Treatment E (crushed IR oxycodone fasted);
- Treatment C (chewed Oxycodone DETERx HFHC) versus Treatment E (crushed IR oxycodone fasted);
- Treatment D (chewed Oxycodone DETERx fasted) versus Treatment E (crushed IR oxycodone fasted);
- Treatment C (chewed Oxycodone DETERx HFHC) versus Treatment A (intact Oxycodone DETERx HFHC);
- Treatment B (intact Oxycodone DETERx fasted) versus Treatment A (intact Oxycodone DETERx HFHC);
- Treatment D (chewed Oxycodone DETERx fasted) versus Treatment A (intact Oxycodone DETERx HFHC);
- Treatment D (chewed Oxycodone DETERx fasted) versus Treatment B (intact Oxycodone DETERx fasted);
- Treatment D (chewed Oxycodone DETERx fasted) versus Treatment C (chewed Oxycodone DETERx HFHC)

Time of maximum plasma concentration (T_{max}) was analyzed using a nonparametric analysis without transformation. The 25% Quantile (Q1), 50% Quantile (Median), and 75% Quantile (Q3) were calculated from the Walsh averages of the treatment differences. The Wilcoxon Signed Rank Test was used to compare T_{max} among the different treatments.

Safety Analyses: Adverse event data, clinical laboratory test results, and physical examination findings, vital signs measurements, and oxygen saturation data were presented descriptively using summary tables and listings. Urine drug screen, breath alcohol test, pregnancy test and 12-lead ECG results were listed. Change and shift from baseline in clinical laboratory results were presented descriptively using summary tables.

Reference ID: 4161285

Subject Disposition and Demographics

Seventy-five (75) subjects entered the Double-blind Treatment Phase and 52 (69.3%) subjects completed all Treatment Periods and were included in the PD Population. A total of 71 subjects comprised the PK population. and all 75 subjects were included in the Safety Population. Most subjects were male (82.7%) and Black or African American (78.7%): all subjects used opioids recreationally per protocol and ranged in age between 19 and 46 years.

Results are discussed in the summary of clinical pharmacology assessment in section 2.

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/s/

SRIKANTH C NALLANI
10/02/2017

YUN XU
10/02/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 208090/S-004

OTHER REVIEW(S)

Division of Anesthesia, Analgesia, and Addiction Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 208090 / S-004

Name of Drug: XTAMPZA (oxycodone) extended-release capsules

Applicant: Collegium Pharmaceutical, Inc.

Labeling Reviewed

Submission Date: October 4, 2016

Receipt Date: October 4, 2016

Last Approved Label: June 7, 2017 (Supplement 005)

Background and Summary Description:
The Sponsor proposed changes to the abuse-deterrent language in the **DRUG ABUSE AND DEPENDENCE** section of the product label.

The proposed revision is reflected in this review and in the PI.

Review

Additions to the package insert when compared with the last approved label are shown below in underline. Deletions are shown in strikeout.

Package Insert

(b) (4)

12 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

[redacted]

Recommendations

The Division has agreed to these proposed changes to the package insert label.

Selma Kraft, PharmD	November 7, 2017
Regulatory Project Manager	Date
Parinda Jani	November 8, 2017
Chief, Project Management Staff	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SELMA S KRAFT
11/08/2017

PARINDA JANI
11/08/2017

EXCLUSIVITY SUMMARY

NDA # 208090 SUPPL # 004 HFD # 170

Trade Name XTAMPZA ER

Generic Name oxycodone hydrochloride extended-release capsules

Applicant Name Collegium Inc

Approval Date, If Known November 6, 2017

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE8

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

The supplement proposes the addition of comparative safety claim regarding PK for Xtampza ER in either intact or manipulated conditions compared to OxyContin. The supplement contains data from a Category 2 pharmacokinetic study, CP-OXYDET-29,

"An Evaluation of the Effect of Tampering on Oxycodone DETERx Compared with OxyContin."

c) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

d) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDAs 021011, 022272, 209777, 202080. For additional NDAs/ANDs, refer to the Orange Book.

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☒ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

1. CP-OXYDET-29: An Evaluation of the Effect of Tampering on Oxycodone DETERx® Compared with OxyContin®
2. CP-OXYDET-28: Assessment of the Oral Human Abuse Liability and Pharmacokinetics of Oxycodone DETERx®

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 075786 YES ☒ ! NO ☐
! Explain:

Investigation #2

IND #075786 YES ☒ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Selma Kraft
Title: Regulatory Health Project Manager
Date: 10/18/17

Name of Division Director signing form: Sharon Hertz, MD
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SELMA S KRAFT
11/06/2017

SHARON H HERTZ
11/06/2017

505(b)(2) ASSESSMENT

Application Information		
NDA # 208090	NDA Supplement #: S- 004	Efficacy Supplement Type SE- 08
Proprietary Name: Xtampza ER Established/Proper Name: Oxycodone extended-release capsules Dosage Form: capsules Strengths: 9 mg, 13.5 mg, 18 mg, 27 mg, 36 mg		
Applicant: Collegium Pharmaceutical		
Date of Receipt: October 4, 2016		
PDUFA Goal Date: November 4, 2017	Action Goal Date (if different): November 3, 2017	
RPM: Selma Kraft		
Proposed Indication(s): Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Reference ID: 4176490

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
NDA 022272 – OxyContin	*FDA's previous finding of safety and effectiveness, clinical pharmacology findings (indication, dosage and administration, contraindications, warnings and precautions, adverse reactions, use in specific populations, drug abuse and dependence, overdosage, clinical pharmacology, noclinical toxicology)*
Published literature	*Nonclinical toxicology—safety of excipients*

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature[1]. See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.

- The sponsor conducted two bioavailability studies, CP-OXYDET-15 and CP-OXYDET-18, between the proposed product and OxyContin. CP-OXYDET-15 is a single dose relative BA study between the proposed product and OxyContin; CP-OXYDET-18 is a multiple dose relative BA study between the proposed product and OxyContin.

- Safety assessment of excipients is based, in part, on published papers of toxicity studies of several components of beeswax and carnauba wax, safety of myristic acid and hypromellose (b) (4)

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES ☒ NO ☐

*If "**NO**," proceed to question #5.*

Reference ID: 4176490

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☒

*If "**NO**", proceed to question #5.*
*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
OxyContin	22272	yes

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☐ YES ☒ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*
*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:
   a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

   b) Approved by the DESI process?

Reference ID: 4176490

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES ☐ NO ☒

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

Abuse deterrent properties, extended-release microspheres

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity,*

disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☒ NO ☐

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☒ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ YES ☒ NO ☐

Reference ID: 4176490

If this application relies only on non product-specific published literature, answer "N/A"
*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s): NDAs: 22272, *200534, 200535, 201194, 202080, 21011*

ANDAs: 202773,20310, 203823, 203107, 204752, 204979, 204092, 204085, 204603, 203208, 20403, 202537, 206456, 76636, (b) (4), (b) (4), *202160, 91393, 91313, 90895, 76758, 77290, 91490, 90659, 77712, 21011*

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): **7674799, 7674800, 7683072, 7776314, 8309060, 8808741, 8894987, 8894988, 9060976, 9073933, 9492389, 9492391, 9492392, 9492393, 9522919, 9675610, 9763933, 9770416, 9775808**

No patents listed ☐ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☒ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

Reference ID: 4176490

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☒ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
7674799, 7674800, 7683072, 7776314, 8309060, 8808741, 8894987, 8894988, 9060976,9073933, 9492389, 9492391, 9492392, 9492393, 9522919, 9675610

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☒ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☒ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): *August 28, 2017, 9/29/2017 and 10/31/17*

***Note**, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☒ Patent owner(s) consent(s) to an immediate effective date of approval ☐

NOTE: At time of submission, 45 days has not occurred since receipt of notification.

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/s/

SELMA S KRAFT
11/06/2017

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

******Pre-decisional Agency Information******

Memorandum

Date: **October 10, 2017**

To: Steven Galati, M.D.
Division Anesthesia, Analgesia, Addiction Products (DAAAP)

Selma Kraft, PharmD.
Regulatory Health Project Manager, (DAAAP)

From: Koung Lee, RPh, MS
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, PharmD
Team Leader
OPDP

Subject: OPDP Labeling Comments for XTAMPZA ER (oxycodone) Extended-release Capsules for Oral Administration, CII

NDA: 208090/S-004

In response to DAAAP's consult request dated June 1, 2017, OPDP has reviewed the proposed product labeling (PI) for the supplemental NDA submission for Xtampza ER (oxycodone) extended release capsule for oral administration.

PI: OPDP's comment on the proposed labeling is based on the substantially complete draft PI received by electronic mail from DAAAP on October 2, 2017, and are provided below.

Thank you for your consult. If you have any questions, please contact Koung Lee at (301) 240-402-8686 or Koung.lee@fda.hhs.gov.

37 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

KOUNG U LEE
10/10/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 208090/S-004

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Kraft, Selma

From: Kraft, Selma
Sent: Tuesday, October 24, 2017 5:11 PM
To: Jack Weet
Subject: NDA 208090/S-004 - Patent Certifications

Importance: High

Dear Jack,

Under 21 CFR 314.54(a)(1)(vi), a 505(b)(2) application must contain a patent certification or statement with respect to any relevant patents that claim the listed drug or that claim any other drugs on which the investigations relied on for approval of the application were conducted, or that claim a use for the listed or other drug. Your 505(b)(2) application relies upon the Agency's finding of safety and effectiveness for NDA 22272 for Oxycontin, but does not contain a patent certification or statement with respect to each patent listed in FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book) for the listed drug upon which you rely. Specifically, your application does not contain a patent certification or statement with respect to patents 9763933, 9770416, and 9775808 that are listed in the Orange Book. Please submit an appropriate patent certification or statement with respect to the 9763933, 9770416, and 9775808 patents.

Please note that if you elect to provide a paragraph IV certification (21 CFR 314.50(i)(1)(i)(A)(4)) with respect to this patent, the certification is to be accompanied by a statement that you will comply with the requirements under 314.52(a) with respect to providing a notice to each owner of the patent or their representatives and to the holder of the approved application for the drug product which is claimed by the patent or a use of which is claimed by the patent and with the requirements under 314.52(c) with respect to the content of the notice.

Please submit this information as soon as possible. Kindly confirm receipt of this email.

Thank you.

Sincerely,
Selma Kraft PharmD.
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Food and Drug Administration
Phone: 240.402.9700

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/s/

SELMA S KRAFT
10/24/2017

Kraft, Selma

From:	Kraft, Selma
Sent:	Tuesday, August 15, 2017 1:38 PM
To:	'Jack Weet'
Subject:	NDA 208090/ S-004 - Xtampza ER - Patent Certification

Dear Jack,
It has come to my attention that no updated patent certification was submitted with your efficacy supplement for Xtampza ER (NDA 208090/S-004). Please submit appropriate patent certifications against your listed drug (see the Orange Book for updated patent information) to your efficacy supplement. Please use the same process to patent certify as you did for the original NDA application.

Submit this to your NDA by **Monday August 21, 2017**. Let me know if you have any questions or concerns.

Kindly confirm receipt of this email. Thank you.

Sincerely,
Selma Kraft PharmD.
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Food and Drug Administration
Phone: 240.402.9700

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/s/

SELMA S KRAFT
08/15/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO: **CDER-OPDP-RPM**			FROM: (Name/Title, Office/Division/Phone number of requestor) Selma Kraft, RPM, DAAAP, x2-9700	
REQUEST DATE: 06-01-2017	IND NO.	NDA/BLA NO. 208090/S-004	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)	
NAME OF DRUG: Xtampza ER	PRIORITY CONSIDERATION: Normal		CLASSIFICATION OF DRUG Opioid	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) September 5, 2017
NAME OF FIRM: Collegium Pharmaceuticals			PDUFA Date: November 3, 2017	

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
- ☒ PACKAGE INSERT (PI)
- ☐ PATIENT PACKAGE INSERT (PPI)
- ☐ CARTON/CONTAINER LABELING
- ☐ MEDICATION GUIDE
- ☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
- ☐ ORIGINAL NDA/BLA
- ☐ IND
- ☒ EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT
- ☐ INITIAL PROPOSED LABELING
- ☒ LABELING REVISION

For OSE USE ONLY
- ☐ REMS

EDR link to submission: Application 208090 - Sequence 0071 - 0071 (118) 10/04/2016 SUPPL-4 (Efficacy) /Multiple Categories/Subcategories
(link to the original submission)

Link to division folder for this supplement: \\fdsfs01\ode2\DAAAP\NDA and sNDA\NDA 208090 (Oxycodone DETERx Collegium)\S-004

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

OSE/DRISK ONLY: For REMS consults to OPDP, send a word copy of all REMS materials and the most recent labeling to CDER DDMAC RPM. List out all materials included in the consult, broken down by audience (consumer vs provider), in the comments section below.

COMMENTS/SPECIAL INSTRUCTIONS:
Review of package insert – there is new PK data going into the label that could be the basis for claims by the sponsor.
This efficacy supplement was submitted October 4, 2016. However, a new HAL study was submitted on March 24, 2017, which was considered a major amendment, and the PDUFA date was extended to November 3, 2017.

Labeling Meetings: September 28, 2017, October 12, 2017
Wrap-Up Meeting: September 12, 2017

Once reviewers are assigned, I can forward them the meetings invites. Thank you.

SIGNATURE OF REQUESTER Selma Kraft	
SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) X DARRTs X eMAIL ☐ HAND

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/s/

SELMA S KRAFT
06/02/2017

Kraft, Selma

From:	Kraft, Selma
Sent:	Friday, May 05, 2017 2:34 PM
To:	'Jack Weet'
Subject:	NDA 208090 / S-004 - Xtampza ER - Stats Information Request

Dear Jack,

We are currently reviewing your Clinical Study Report for CP-Oxydet-28 for supplement 004, and have the following information requests:

1. Drug Liking Emax was derived from (b) (4) hours post-dose in your analysis instead of 12 or 24 hours. Please explain if you have specific reason to do so. Several subjects achieved Emax after (b) (4) hours post-dose, such as Subject (b) (4), treatment A, had Emax of 99 at hour 12, while from (b) (4) hours post-dose, the Emax score is 61.

2. On page 89 of the Clinical Study Report, Table 9 shows Inferential Analysis for Drug Liking Emax for Primary Comparisons, in the footnote, you mentioned 'T was statistically lower than C by > (b) (4) points, respectively, using δ* = (b) (4), respectively, the last value prior to non-significance;' Explain how you get the value of (b) (4) and (b) (4).

3. On page 105 of the Clinical Study Report, Table 16 presents the Inferential Analysis Results of PD Parameters for Take Drug Again, and you mentioned in the footnote that, 'Median differences (SEM) are provided using Hodges-Lehman estimates with CIs estimated using Moses methodology, and p-values from the analysis of ranked data.' Please provide SAS code for the analysis of Take Drug Again.

4. On page 90 and 91, Figure 3 and Figure 4 don't match your analysis results. Please verify your graphs.

Please submit responses as soon as possible, but no later than **COB Thursday May 11, 2017.** Kindly acknowledge receipt of this request and let me know if you have any questions. Thank you.

Sincerely,
Selma Kraft PharmD.
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Food and Drug Administration
Phone: 240.402.9700

Reference ID: 4094485

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/s/

SELMA S KRAFT
05/05/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208090 / S-004

REVIEW EXTENSION –
EFFICACY SUPPLEMENT

Collegium Pharmaceutical Inc
780 Dedham Street
Suite 800
Canton, MA 02021

Attention: John F. Weet, PhD
Vice President, Regulatory Affairs and Quality Assurance

Please refer to your Supplemental New Drug Application (sNDA) dated and received October 4, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for XTAMPZA (Oxycodone) ER Capsule.

On March 24, 2017, we received your major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is November 4, 2017.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017. If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by October 7, 2017.

If you have questions, call Selma Kraft, Regulatory Project Manager, at (240)-402-9700.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, MD
Division Director
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

SHARON H HERTZ
04/03/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Controlled Substance Staff
Attn: Sandra Saltz, Corinne Moody,

FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Selma Kraft, for:
Sharon Hertz, M.D. Director, Division of Anesthesia, Analgesia, and
Addiction Products (DAAAP), HFD-170

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
March 3, 2017		208090	Efficacy Supplement (SE8)	October 4, 2016

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Xtampza ER (oxycodone) abuse-deterrent capsules	Standard review clock	Opioid analgesic	Reviews Due June 30, 2017

NAME OF FIRM: **Collegium Pharmaceutical**

REASON FOR REQUEST

I. GENERAL

- ☒ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:

This is a re-consult for this supplement. Originally consulted CSS on 10/3/16 . It was determined that CSS was not needed for the supplement. However, the Sponsor will be submitting an oral HAL study, CP-OXYDET-28, to further support their supplement proposing new language in the Drug Abuse and Dependence section of the package insert.

The sponsor has already provided PK data from a Category 2 study to support these labeling changes; study CP-OXYDET-29, "An Evaluation of the Effect of Tampering on Oxycodone DETERx® Compared with OxyContin."
EDR link: \\CDSESUB1\evsprod\NDA208090\0071
\\CDSESUB1\evsprod\NDA208090\208090.enx

Please review from a CSS perspective and attend scheduled meetings.
Steve Galati is the clinical reviewer (6-7409) and Josh Lloyd is the clinical team leader. Please contact me if you

have any questions.	
SIGNATURE OF REQUESTOR Selma Kraft	METHOD OF DELIVERY (Check all that apply) ☒ DARRTS ☒ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

06/18/2013

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/s/

SELMA S KRAFT
03/03/2017

Kraft, Selma

From: Kraft, Selma
Sent: Monday, February 06, 2017 7:09 AM
To: 'Jack Weet'
Subject: RE: NDA 208090 Xtampza ER S-004

Hi Jack,

Please submit your final clinical study report for study-28 as an amendment to your NDA supplement. You can also submit the summary data ahead of the amendment for the Division to review.
You may consider this a formal request for the above requested items.

Thank you.

Sincerely,
Selma

From: Jack Weet [mailto:jweet@collegiumpharma.com]
Sent: Friday, February 03, 2017 2:19 PM
To: Kraft, Selma
Subject: RE: NDA 208090 Xtampza ER S-004

Hi Selma,
The Clinical Study Report for Study 028 will probably be ready end of February/ early March. We could, however, arrange for summary data, including PK, earlier than that if the Division would be interested in viewing those data in advance of the CSR.

Jack

John F. Weet, PhD
Vice President
Regulatory Affairs and Quality Assurance
COLLEGIUM Pharmaceutical, Inc.
780 Dedham Street, Suite 800
Canton, MA 02021
Tel.: 781.713.3731 | Fax.: 781.828.4697
Mobile: 585-730-1369
Main Tel.: 781.713.3699
jweet@collegiumpharma.com

From: Kraft, Selma [mailto:Selma.Kraft@fda.hhs.gov]
Sent: Friday, February 03, 2017 12:58 PM
To: Jack Weet <jweet@collegiumpharma.com>
Subject: RE: NDA 208090 Xtampza ER S-004

Hi Jack,
This is not a request for a formal submission. We are still discussing what the best course of action is. Do you have an estimated timeline of when the study will be finalized for submission?

Reference ID: 4051659

Thanks,
Selma

From: Jack Weet [mailto:jweet@collegiumpharma.com]
Sent: Friday, February 03, 2017 12:53 PM
To: Kraft, Selma
Subject: RE: NDA 208090 Xtampza ER S-004

Hi Selma,
Thank you for your request. I don't have a firm date for availability. Is there any way that you could formalize your question in form of an IR, specific to the pending S-004? Or should we consider your email a formal request? In any event, we are working diligently to finalize.
Best,

Jack

John F. Weet, PhD
Vice President
Regulatory Affairs and Quality Assurance
COLLEGIUM Pharmaceutical, Inc.
780 Dedham Street, Suite 800
Canton, MA 02021
Tel.: 781.713.3731 | Fax.: 781.828.4697
Mobile: 585-730-1369
Main Tel.: 781.713.3699
jweet@collegiumpharma.com

From: Kraft, Selma [mailto:Selma.Kraft@fda.hhs.gov]
Sent: Friday, February 03, 2017 11:55 AM
To: Jack Weet <jweet@collegiumpharma.com>
Subject: RE: NDA 208090 Xtampza ER S-004

Hi Jack,
Thanks for the background information. Do you have the final complete study report for Study-28? When would you be able to submit it?
Thanks,
Selma

From: Jack Weet [mailto:jweet@collegiumpharma.com]
Sent: Wednesday, February 01, 2017 3:56 PM
To: Kraft, Selma
Cc: Jani, Parinda
Subject: NDA 208090 Xtampza ER S-004

Hi Selma,
As you may be aware, Collegium submitted a supplemental NDA (S-004) on October 4, 2016, which proposed language in Section 9.2 of our package insert. The proposal was to supplement the table which shows the PK of manipulated and intact Xtampza ER after oral administration with comparative results for the PK of manipulated and intact OxyContin. The purpose of this comparison was to show that crushing Xtampza ER had (b) (4) on the oral PK of the drug compared to taking it intact, whereas crushing OxyContin converted the extended-release PK profile into that of an immediate release oxycodone. Note that this comparative PK data was generated in two studies which had nearly

identical results: Study CP-OXYDET-25 (submitted in the original NDA) and in a recently completed replicate Study CP-OXYDET-29. The data from Study -29 was submitted in support of the S-004 and proposed label change.

As part of the filing review of S-004, the Division requested a teleconference on November 28, 2016. In this teleconference, the Division requested clarification of the intent of our submission given that (b) (4) Collegium clarified that the observed pharmacokinetic findings have potential safety implications. The Division requested that Collegium therefore provide a clinical safety justification as to why the PK differences were important; on December 12, 2016, Collegium submitted a clinical information amendment as a result of this verbal Information Request. In addition to the clinical justification requested on November 28, Dr. Hertz inquired about the status of CP-OXYDET-28, a clinical abuse potential study for the oral route of abuse in progress with Xtampza ER. Dr. Hertz further commented that the results of this clinical abuse potential study could further inform the review of S-004 and the requested label change.

At this time, Study -28 is complete. Our question at this time is whether the Division would want to request submission of the Study -28 data, as previously discussed. We can submit these data if requested in an IR, as an amendment to S-004. The results of the study were positive, showing statistically significant reductions in Drug Liking and Take Drug again for manipulated and intact Xtampza versus the IR control, and we believe they may be informative in the Division's review.

Please advise the Division review team, and let Collegium know of their response at your earliest convenience.

Thanks and regards,

Jack
John F. Weet, PhD
Vice President
Regulatory Affairs and Quality Assurance
COLLEGIUM Pharmaceutical, Inc.
780 Dedham Street, Suite 800
Canton, MA 02021
Tel.: 781.713.3731 | Fax.: 781.828.4697
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/s/

SELMA S KRAFT
02/06/2017

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 28, 2016

THROUGH: Ellen Fields, MD, MPH; Deputy Director

SUBJECT: Tcon to discuss adequacy of PK data to support labeling changes to Section 9.2 of product labeling

APPLICATION/DRUG: NDA 208090 S-004/Xtampza ER

Teleconference Attendees:

FDA:
Sharon Hertz, MD; Director
Ellen Fields, MD, MPH; Deputy Director
Srikanth Nallani, PhD; Clinical Pharmacology Reviewer
Yun Xu, PhD; Clinical Pharmacology Team Leader
James Tolliver; Reviewer, Controlled Substance Staff

Sponsor:
Mike Heffernan, Founder and CEO
Ernest Kopecky VP, Clinical Development
Alison Fleming, VP, Product Development
Jack Weet, VP, Regulatory Affairs and Quality Assurance

The Division requested a teleconference with the sponsor to discuss the adequacy of the data submitted in a prior approval supplement (PAS) 004 to support changes to the Drug Abuse section of the product labeling. The supplement proposes the addition of comparative safety claim regarding PK for Xtampza ER in either intact or manipulated conditions compared to OxyContin.

The sponsor submitted a PAS on October 4, 2016 which contains data from a Category 2 pharmacokinetic study, CP-OXYDET-29, "An Evaluation of the Effect of Tampering on Oxycodone DETERx Compared with OxyContin." This study replicates study CP-OXYDET-25 which was submitted to the original NDA, however, during the review the original submission the Division determined that (b) (4)

(b) (4).

Supplement 004 makes reference to a teleconference held between the Sponsor and the Division on October 23, 2015. The Sponsor believed that the Division recommended that they replicate study CP-OXYDET-25 in order to (b) (4) During the teleconference held on November 28, 2016, the Division clarified that comparative PK data alone without data that demonstrate a pharmacodynamic correlation would not be sufficient to support inclusion of a comparative safety claim in the product labeling. The Division further clarified that the Sponsor was asked during the October 23, 2015 conference to replicate the PK study and include PD endpoints and that a (b) (4) Regarding Supplement 004, the Sponsor was encouraged to provide a clinical rationale to support inclusion of the comparative safety claim based on PK data alone. The Sponsor's submission should discuss why the PK differences between Xtampza ER and OxyContin are meaningful and support a clinical safety claim. The Sponsor agreed to provide a clinical rationale as an amendment to the PAS.

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/s/

AYANNA S AUGUSTUS
01/23/2017

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 9, 2016

FROM: Ayanna Augustus, PhD, RAC, Senior Regulatory Health Project Manager

SUBJECT: Controlled Substance Staff Consult Request

APPLICATION/DRUG: NDA 208090/ Xtampza ER

On October 6, 2016, a consult request was issued to the Controlled Substance Staff to review and provide comment on prior approval labeling supplement S-004 for Xtampza ER which proposes to revise section 9.2 of the product labeling. Following review of the contents of the submission and discussion with the CSS reviewer, the Division has determined that a consult review by CSS is not needed as the Sponsor is requesting a (b) (4)

This memo closes the CSS consult request.

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/s/

AYANNA S AUGUSTUS
12/09/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Controlled Substance Staff
Attn: Sandra Saltz, Corinne Moody, Michael Klein

FROM (*Name, Office/Division, and Phone Number of Requestor*): Lisa Ayanna Augustus, PhD, RAC, RPM, for:
Sharon Hertz, M.D.
Acting Director, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP), HFD-170

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
October 6, 2016		208090	Labeling Supplement/PAS	October 4, 2016

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Xtampza ER (oxycodone) abuse-deterrent capsules	Standard review clock	Opioid analgesic	March 3, 2017

NAME OF FIRM: **Collegium Pharmaceutical**

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☒ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Collegium submitted a prior approval labeling supplement proposing new language in the Drug Abuse and Dependence section of the package insert. The sponsor has provided PK data from a Category 2 study to support these labeling changes; study CP-OXYDET-29, "An Evaluation of the Effect of Tampering on Oxycodone DETERx® Compared with OxyContin."
EDR link: \\CDSESUB1\evsprod\NDA208090\0071
\\CDSESUB1\evsprod\NDA208090\208090.enx
Please review from a CSS perspective and attend scheduled meetings.
Steve Galati is the clinical reviewer (6-7409) and Pam Horn (6-5315) is the clinical team leader. Please contact me if you have any questions.

SIGNATURE OF REQUESTOR
Ayanna Augustus, RPM

METHOD OF DELIVERY (Check all that apply)
☒ DARRTS ☐ EMAIL ☐ MAIL ☐ HAND

Reference ID: 3986089

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/s/

AYANNA S AUGUSTUS
10/06/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208090/S-004

ACKNOWLEDGMENT --
PRIOR APPROVAL SUPPLEMENT

Collegium Pharmaceuticals, Inc.
780 Dedham Street
Suite 800
Canton, MA 02021

Attention: John Weet, PhD
Vice President, Regulatory Affairs and Quality Assurance

Dear Dr. Weet:

We have received your supplemental New Drug Application (sNDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 208090

SUPPLEMENT NUMBER: S-004

PRODUCT NAME: Xtampza ER (oxycodone) extended release Capsules

DATE OF SUBMISSION: October 4, 2016

DATE OF RECEIPT: October 4, 2016

This supplemental application proposes changes to the abuse-deterrent language in the **DRUG ABUSE AND DEPENDENCE** section of the product label.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 3, 2016, in accordance with 21 CFR 314.101(a).

If the application is filed, the goal date will be April 4, 2017.

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i) in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action.

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia and Addiction Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have questions, call me, at (301) 796-3980.

Sincerely,

{See appended electronic signature page}

Ayanna Augustus, PhD, RAC
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

AYANNA S AUGUSTUS
10/06/2016