CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208653Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sharon Hertz, MD
Subject	Division Director Summary Review
NDA #	208653
Applicant Name	KemPharm, Inc.
Date of Submission	August 23, 2018
PDUFA Goal Date	February 23, 2018
Proprietary Name / Established (USAN) Name	Apadaz Benzhydrocodone/Acetaminophen Tablets
Dosage Forms / Strength	Tablet/ 6.12 mg Benzhydrocodone/ 325 mg Acetaminophen
Proposed Indication(s)	The short-term (no more than 14 days) management of acute pain
Action:	Approval

Material Reviewed/Consulted From First Cycle Review OND Action Package, including:	
Medical Officer Review	Jacqueline Spaulding, MD; Pamela Horn, MD
Pharmacology Toxicology Review	Marcus Delatte, PhD; Elizabeth Bolan, PhD; R. Daniel Mellon, PhD
OPQ Review	Benjamin Stevens, PhD, Donna Christner, PhD;, Ciby Abraham, PhD, Steven Kinsley, PhD; Christina Capacci-Daniel, PhD.; Derek Smith, PhD.; Shujun Chen, PhD; Pei-I Chu, PhD; Mei Ou, PhD.; Haritha Mandula, Ph.D.
Clinical Pharmacology Review	Suresh Naraharisetti, PhD, Yun Xu, PhD
Controlled Substances Staff	James Tolliver, PhD, Silvia Calderon; Ling Chen, PhD; Qianyu Dang, PhD
OSE/DMEPA	James Schlick, MBA, RPh, Vicky Borders-Hemphill, PharmD
OSE/DEPI	Jana McAninch, MD MPH MS, Alex Secora, MPH, Cynthia Kornegay, PhD; Kunthel By, PhD; Mark Levenson; PhD; Jennie Wong, PharmD; Rajdeep Gill, PharmD; Grace Chai, PharmD
OPDP/DCDP	L. Shenee Toombs, PharmD
OMP/DMPP	LaShawn Griffiths, MSHS-PH, BSN, RN, Barbara Fuller, RN, MSN, CWOCN, Morgan Walker, PharmD, MBA

Material Reviewed/Consulted For Second Cycle Review OND Action Package, including:	
Pharmacology Toxicology Review	Marcus Delatte, PhD; Newton Woo, PhD; R. Daniel Mellon, PhD
OPQ Review	Xiaobin Shen, PhD, Julia Pinto, PhD
Clinical Pharmacology Review	Suresh Naraharisetti, PhD, Yun Xu, PhD
Controlled Substances Staff	James Tolliver, PhD; Silvia Calderon, PhD; Dominic Chiapperino, PhD
OSE/DMEPA	James Schlick, MBA, RPh, Otto Townsend, PharmD
OPDP/DCDP	L. Shenee Toombs, PharmD
OMP/DMPP	LaShawn Griffiths, MSHS-PH, BSN, RN, Barbara Fuller, RN, MSN, CWOCN, Morgan Walker, PharmD, MBA
OSE/DRISK	LaShaun Washington-Batts, PharmD; Joan Blair, RN, MPH; Selena Ready, PharmD; Cynthia LaCivita, PharmD,

OND=Office of New Drugs OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Errors Prevention OSI=Office of Scientific Investigations
OPDP=Office of Prescription Drug Promotion DCDP=Division of Consumer Drug Promotion
OMP=Office of Medical Policy Initiatives DMPP=Division of Medical Policy Programs

Signatory Authority Review Template

1. Introduction

This is the second cycle review for a 505(b)(2) application submitted by KemPharm Inc. for Apadaz (benzhydrocodone and acetaminophen) capsules, an immediate-release formulation with properties intended to deter abuse by the intranasal and intravenous routes of administration. The purported abuse-deterrent properties were based on (b) (4) [redacted] The Applicant received a Complete Response (CR) letter for the first review cycle on June 10, 2016, because the agency reviewers concluded that the results of the in vitro and in vivo studies did not support a finding that there were any abuse-deterrent properties for Apadaz and the Applicant would not agree to the labeling edits from agency reviewers. Specifically, the CR letter described the deficiency as:

> "The proposed labeling in Section 9.2, (b) (4) [redacted] does not accurately convey the outcome of the studies submitted, and therefore, is false and misleading. Therefore, according to 21 CFR 314.125(b)(6) the application may not be approved.
>
> To address this deficiency, submit labeling that accurately conveys the results of the assessment of abuse-deterrent properties and that conveys that there is no clinically relevant difference from the non abuse-deterrent comparator."

Following the CR action, the Applicant submitted three Formal Dispute Resolution Requests (FDRRs) (b) (4) [redacted]

In the current submission, the Applicant has provided amendments to the drug substance specifications, product stability data to support blister packaging, and an additional in vitro abuse-deterrent extraction study report. Sections of this memo have been taken from my June 10, 2016, summary memo.

2. Background

The application is submitted under 505(b)(2) based on referencing the agency's prior findings of for NDA 20716, Vicoprofen (hydrocodone and ibuprofen), and NDA 21123, Ultracet (tramadol and acetaminophen). The primary development goal for Apadaz was to reduce the intranasal (IN) and oral abuse potential of immediate-release (IR) hydrocodone/acetaminophen products.

The drug substance was formulated with a benzyl group attached to a hydrocodone molecule by an ester bond, creating a hydrocodone prodrug (benzhydrocodone, called KP201 during development and in sections of this review), which is hydrolyzed to hydrocodone and benzoic acid in the presence of esterases in the gastrointestinal system or blood.

In the original submission, the Applicant provided product-specific chemistry, manufacturing, and controls (CMC) information. Nonclinical support for hydrocodone is based on reliance on the Agency's previous findings for the referenced drug, Vicoprofen, and for acetaminophen hydrochloride, on the Agency's previous findings for the referenced drug, Ultracet. The Applicant provided adequate nonclinical data to support benzhydrocodone and the formulation, including novel excipients and excipients that exceed the amount present in the Inactive Ingredients Guide. Support for the clinical efficacy and safety of the benzhydrocodone and acetaminophen in Apadaz is based in part on reliance on the Agency's previous findings for the referenced drugs using relative bioavailability studies as the scientific bridge for doing so. Bioequivalence to the hydrocodone and acetaminophen in Norco, a marketed product containing hydrocodone bitartrate and acetaminophen, is used to demonstrate that the combination is not novel and does not require factorial design efficacy studies as described in 21 CFR 300.50. The Applicant conducted in vitro and in vivo studies to evaluate the abuse-deterrent properties of the formulation. An advisory committee was convened to discuss this application on the May 5, 2016.

As described in the Guidance for Industry, Abuse-Deterrent Opioids – Evaluation and Labeling[1], the development of abuse-deterrent formulations of opioid analgesics is recognized by FDA as an important approach to reducing abuse of prescription opioids. Prescription opioid products are an important component of modern pain management. However, abuse and misuse of these products have created a serious and growing public health problem. One potentially important step towards the goal of creating safer opioid analgesics has been the development of opioids that are formulated to deter abuse. FDA considers the development of these products a high public health priority.

In general, the primary route of abuse of opioid analgesics is oral, followed by different frequencies of intranasal and intravenous abuse depending on the specific product. This is true for both immediate-release and extended-release products. It is important to remember that even when a product has abuse-deterrent properties that may reduce abuse by one or several routes, it does not mean that there is no risk of abuse or addiction. It means, rather, that the risk of abuse by certain routes is lower than it would be without the abuse-deterrent properties. Abuse-deterrent is not synonymous with abuse-proof. The currently approved abuse-deterrent opioid analgesics (listed in the next paragraph) all remain in schedule II of the Controlled Substances Act because the risk for addiction has not been reduced by the presence of abuse-deterrent characteristics.

[1] http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm334743.pdf

There is currently one immediate-release product labeled with abuse-deterrent properties as described in the guidance, Roxybond (oxycodone hydrochloride) tablets.[2] There are 10 approved extended-release/long-acting opioid analgesic products with labeling language describing studies conducted in support of abuse-deterrent properties; OxyContin (oxycodone extended-release tablets), Targiniq (oxycodone and naloxone extended-release tablets), Embeda (morphine sulfate and naltrexone extended-release capsules), Hysingla ER (hydrocodone extended-release tablets), Morphabond (morphine sulfate extended-release tablets), Xtampza ER (oxycodone hydrochloride extended-release capsules), Troxyca ER (oxycodone hydrochloride and naltrexone extended-release capsules), Arymo ER (morphine sulfate extended-release tablets), and Vantrela ER (hydrocodone extended-release tablets).

To date, none of the abuse-deterrent opioid analgesic products has submitted data to support a finding of an actual effect on reducing abuse of the product using currently available post-marketing data. Although such claims have been made in publications, no data have been provided to FDA to support such a finding, suggesting the possibility that the data are not adequate to meet regulatory standards to support labeling or a claim.[3] Difficulty in demonstrating an effect on abuse of products with abuse-deterrent properties may be due, in part, to an inability to distinguish the effects of the abuse-deterrent formulation from active federal, state, and local efforts to reduce prescription opioid abuse that underlie reductions in abuse of prescription opioids more broadly, including non abuse-deterrent formulations.

Abuse-deterrent formulations may have unintended consequences with a negative impact on public health. As discussed at a Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee, held on March 13 and 14, 2017, Opana ER, an extended-release formulation of oxymorphone, was developed to be abuse deterrent.[4] The agency did not find the pre-marketing data supportive of a potential abuse-deterrent effect and did not permit labeling to describe abuse-deterrent properties. However, as described in the materials and discussion at the advisory committee meeting, the change in formulation did result in a change in behaviors associated with abuse resulting in an outbreak of HIV in one community, and a thrombocytopenic microangiopathy in a number of abusers. Further, there appeared to be a shift from nasal route of abuse to the riskier intravenous route of abuse. The committee voted that the benefits of this formulation no longer outweighed its risk. In response to a request by the agency, Opana ER has been withdrawn from the market. Another unintended consequence that has been identified is that some of the abuse-deterrent formulations become sticky when wet, resulting in tablets getting stuck in the esophagus, or causing obstructions in the gastrointestinal tract. These findings resulted in labeling instructions for patients to take these tablets with a cup of water and not to pre-wet the tablets.

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[2] Oxaydo (oxycodone immediate-release tablets) was approved June, 2011. There is a description of studies evaluating whether the formulation might have an abuse-deterrent effect in Section 12 of the labeling as the approval pre-dates the publication of the guidance.

[3] Coplan PM, Chilcoat HD, Butler SF, Sellers EM, Kadakia A, Harikrishnan V, Haddox JD , Dart RC The effect of an abuse-deterrent opioid formulation (OxyContin) on opioid abuse-related outcomes in the postmarketing setting. Clin Pharmacol Ther. 2016 Sep;100(3):275-86. doi: 10.1002/cpt.390. Epub 2016 Jun 22.

[4] See: https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/ucm545759 htm

3. CMC and Biopharmaceutics

There were no CMC deficiencies described in the CR letter from the first review cycle. However, in the current submission, the Applicant provided additional information, as described in the OPQ review dated January 3, 2018:

> a) The benzhydrocodone HCl drug substance specifications have been tightened in both this NDA and the corresponding drug substance DMF, as requested and agreed upon in the prior review cycle.
>
> b) Acceptable product stability data collected from tablets packaged in blisters has been provided to support the addition of blister packaging.
>
> c) An additional in vitro abuse deterrent extraction study report has been provided. The study tested the different extraction efficiency of the benzhydrocodone HCl and APAP from the test product in comparison to the reference product hydrocodone/APAP tablet. The study supports its related in vitro extraction language in Section 9 of the package insert although the study itself is not meaningful. This has no impact to the product quality itself. Hence it does not affect a review recommendation from the CMC perspective.
>
> d) The product prescribing information has been revised to address outstanding deficiencies from the prior review cycle. The edits have been made in conjunction with review teams from other disciplines.

The following is from my original summary memo dated June 10, 2016:

> The drug product is an immediate-release formulation containing 6.67mg of benzhydrocodone hydrochloride, a benzyl ester prodrug of hydrocodone and 325mg of acetaminophen. Benzhydrocodone hydrolyzes to the active hydrocodone and benzoic acid. The drug substance benzhydrocodone is referenced to a new DMF (b) (4) and has been found to be adequate. Benzhydrocodone drug substance contains impurities (b) (4) which is a structural alert for mutagenicity. As noted by Dr. Delatte in the pharm/tox review:
>
> > "Other than (b) (4) which contains a structural alert for mutagenicity, the proposed specifications are within ICH Q3A(R2) guidelines. For (b) (4) the Applicant has proposed a specification of NMT (b) (4) %. At this specification, a person would be exposed to (b) (4) mcg/day. This is acceptable as per ICH M7 for the proposed acute indication.
> >
> > Of note, an additional drug substance impurity (b) (4) (b) (4) was identified by our CMC review team during the review of the DMF. The levels of this impurity, which is not specified by the Applicant in the drug

product, are controlled at the level of the drug substance by the DMF holder and specified to be within the levels recommended by ICH M7."

The drug substance acetaminophen is referenced to DMF [redacted] which has been referenced by a number of approved drug products and has been previously reviewed and found to be adequate. As noted by Dr. Delatte, drug substance specifications list [redacted] impurities for acetaminophen that have structural alerts for mutagenicity: [redacted] Regarding these impurities, Dr. Delatte notes the following:

[redacted]

There are no novel excipients in the drug product. As noted by Dr. Delatte, "The KP201-related drug product specifications are consistent with the ICH Q3B(R2) qualification thresholds and are acceptable. The only drug product degradant specified related to acetaminophen is [redacted] At the proposed specification and at the maximum daily dose of 3900 mg/day acetaminophen via this drug product, a person would ingest [redacted] mcg [redacted] The proposed specification is within that of the referenced drug product, therefore it is acceptable based on the Agency previous finding of safety."

As noted by the biopharmaceutics reviewer, the in vitro dissolution method for the drug product "was derived directly from the USP monograph for Hydrocodone Bitartrate and Acetaminophen Tablets. The dissolution method of KP201 had been determined in buffers with different pH conditions. This method also showed that the dissolving conditions of acetaminophen matched those in the USP monograph. Therefore, the proposed dissolution method as Apparatus II (paddle), 0.1N HCl, 900 mL, 50 rpm, is acceptable for the drug product." The in vitro dissolution method was adequately validated, and the mean and individual dissolution data were acceptable for the drug product.

The CMC microbiology review found the drug product to be a low microbial risk solid oral tablet, (b) (4) and found the Applicant's request for waiver of microbial limit testing (MLT) specifications for drug product release and stability specifications acceptable. The Applicant has committed to MLT and (b) (4) tests on these stability batches annually and to report additional stability data from these studies in post-approval Annual Reports to the NDA.

The tablets are stored in HDPE bottles (b) (4)

The facilities, the site responsible for drug product manufacture, packaging and labeling, and release and stability testing, is (b) (4) As noted in the CMC review (b) (4):

(b) (4)

The response to the information request was adequate and the reviewer concluded that "based on the acceptable inspectional history of this facility, their experience with these unit operations, and the adequate IR responses received, (b) (4) is **acceptable** for NDA 208653."

The final conclusion for this second review cycle is that sufficient data were provided to support the quality and safety of the manufacture and release of the drug substance and drug product. I concur with the conclusions reached by the chemistry review team regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 36 months for tablets packaged in the HDPE

bottles when stored at 20 – 25 °C (68 –77 °F) with excursions permitted between 15 – 30 °C (59 – 86°F). Stability testing only supports an expiry of 12 months for tablets packaged in blister strips under the same storage conditions. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical data were submitted. The following is from my first cycle review:

The following is from Dr. Delatte's review:

> "The Applicant submitted 14- and 28-day repeat-dose toxicology studies in the rat and dog and the fully battery of genetic toxicology studies for KP201 and its comparator drug hydrocodone bitartrate. The toxicological profile of KP201 was consistent with the expected toxicological profile of hydrocodone and the drug product does not appear to present any different safety profile from comparable generic drug products containing hydrocodone and acetaminophen.
>
> In regard to the genetic toxicology studies conducted, in vitro findings demonstrated that KP201 was positive for the induction of structural chromosomal aberrations in the S9-activated test system at the four-hour exposure time point; whereas it was negative under all other conditions in this assay. KP201 was not mutagenic in the Ames assay. KP201 and hydrocodone bitartrate in male rats were both negative in the in vivo micronucleus and comet assays.
>
> Overall, there are no unique safety concerns with the KP201 component of this product given that the excipients (including benzoic acid coupled to hydrocodone to make the prodrug) used in the benzhydrocodone/APAP drug combination do not exceed that used in FDA-approved products and the toxicity profiles for KP201 overlap with that of hydrocodone bitartrate."

Regarding pediatric studies, Dr. Delatte notes the following:

> "As per the agreed Pediatric Study Plan (PSP), the Applicant will conduct a juvenile animal study to assess the impact of benzhydrocodone to support pediatric studies in neonates and infants aged 0 to < 2 years. This study will be as a post marketing requirement. Final agreement on the study protocol will be obtained from the Agency prior to study initiation."

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology

The following is from my first cycle review:

No new clinical pharmacology studies were submitted for review during the second review cycle. The following section is from my first cycle review.

The Applicant submitted five clinical pharmacokinetic studies in support of the application in the original submission:

- KP201.105: Relative bioavailability study of KP201/acetaminophen tablet to Vicoprofen tablet with respect to hydrocodone under fasted condition
- KP201.106: Relative bioavailability study of KP201/acetaminophen tablet to Ultracet tablet
  with respect to acetaminophen under fasted condition
- KP201.102: Bioequivalence study of KP201/acetaminophen tablet to Norco tablet, 7.5 mg/325 mg under fasted condition
- KP201.104: Effect of food on the bioavailability and pharmacokinetic of hydrocodone and acetaminophen from KP201/acetaminophen tablet, and the relative bioavailability of KP201/acetaminophen to Norco tablets under fed condition
- KP201.103: Single- and multiple-dose pharmacokinetics of KP201/acetaminophen

In all human pharmacokinetic studies following oral administration of the drug product, plasma concentrations of KP201 were below the limit of quantitation of 25 pg/mL.

Benzhydrocodone levels were measureable in plasma following intranasal administration of the crushed product in human abuse liability studies. The median T_{max} range of KP201 was 0.46 to 0.73 hours post-dose. The half-life of KP201 was short, ranging from 1 to 1.48 hours. Mean C_{max} and AUC values for KP201 increased with an increase in dose. The mean C_{max} and AUC_{inf} for KP201 ranged from 9.4 ± 2.8 ng/mL and 7.6 ± 2.4 h·ng/mL (KP201/acetaminophen 6.67/325 mg, crushed) to 27.0 ± 25.7 ng/mL and 26.1± 20.6 h·ng/mL (KP201/acetaminophen 26.68/1300 mg, crushed).

KemPharm is relying on the FDA's findings of efficacy and safety for two listed drugs, Vicoprofen (7.5 mg hydrocodone bitartrate/ 200 mg ibuprofen oral tablet; NDA 020716), and Ultracet (37.5 mg tramadol hydrochloride/325 mg acetaminophen oral tablet; NDA 021123). To establish the scientific bridge for relying on the Agency's findings of safety and efficacy for the two listed drugs, two relative bioavailability studies were conducted in the fasted state comparing KP201/acetaminophen with Vicoprofen for hydrocodone (Study KP201.105) and Ultracet for acetaminophen (Study KP201.106). KP201/acetaminophen met the bioequivalence criteria for AUC and C_{max} for hydrocodone compared to Vicoprofen, and for acetaminophen compared to Ultracet. The details of these two studies can be found in Dr. Naraharisetti's review.

As discussed in the background, KP201/acetaminophen was compared to Norco (7.5 mg hydrocodone bitartrate/ 325 mg acetaminophen) to support that the delivery of hydrocodone and acetaminophen from KP201/ acetaminophen does not represent a novel combination. Study

KP201.102 compared the plasma concentrations versus time profiles for hydrocodone and acetaminophen following a single dose of KP201/ acetaminophen and a single dose of Norco administered orally under fasted conditions in 23 subjects. The following figure and table from Dr. Naraharisetti's first cycle review shows that the exposure to hydrocodone and acetaminophen were bioequivalent to Norco. Bioequivalence criteria were met for both hydrocodone and acetaminophen. Beyond C_{max} and AUC, it can also be seen from the figures that the T_{max} values are nearly identical for both hydrocodone and acetaminophen (APAP) in the fasted state.

Figure 1: Mean ± SD plasma hydrocodone (left figure) and acetaminophen (right figure) concentration-time profiles (0-24 h) following administration of single doses of KP201/acetaminophen and Norco to healthy subjects under fasted conditions (Study KP201.102)

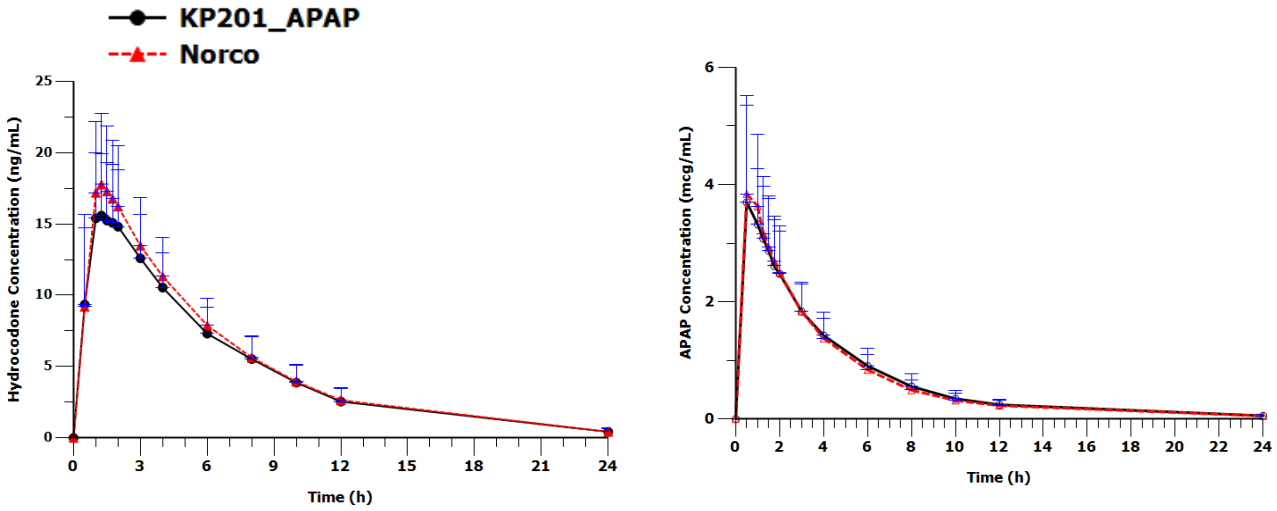


Table 1: Study KP201.102: Relative bioavailability of hydrocodone from KP201/acetaminophen and Norco under fasted conditions

Parameter	Geometric Mean [a]		Geometric Mean Ratio [%]	
	Test	Reference	Estimate	90% Confidence Interval (Lower, Upper)
KP201/APAP, 6.67 mg/325 mg vs. Norco, 7.5 mg/325 mg				
Cmax	16.27	18.75	86.79	81.38 , 92.56
AUC0-t	108.01	114.70	94.17	89.99 , 98.54
AUCinf	111.76	118.83	94.05	90.32 , 97.94

[a] Least squares geometric means, based on the analysis of natural log-transformed data.

Table 2: Study KP201.102: Relative bioavailability of acetaminophen from KP201/acetaminophen and Norco under fasted conditions

Parameter	Geometric Mean [a]		Geometric Mean Ratio [%]	
	Test	Reference	Estimate	90% Confidence Interval (Lower, Upper)
KP201/APAP, 6.67 mg/325 mg vs. Norco, 7.5 mg/325 mg				
Cmax	3.79	4.18	90.76	79.81 , 103.20
AUC0-t	15.82	15.64	101.15	98.08 , 104.32
AUCinf	16.76	16.63	100.76	97.66 , 103.96

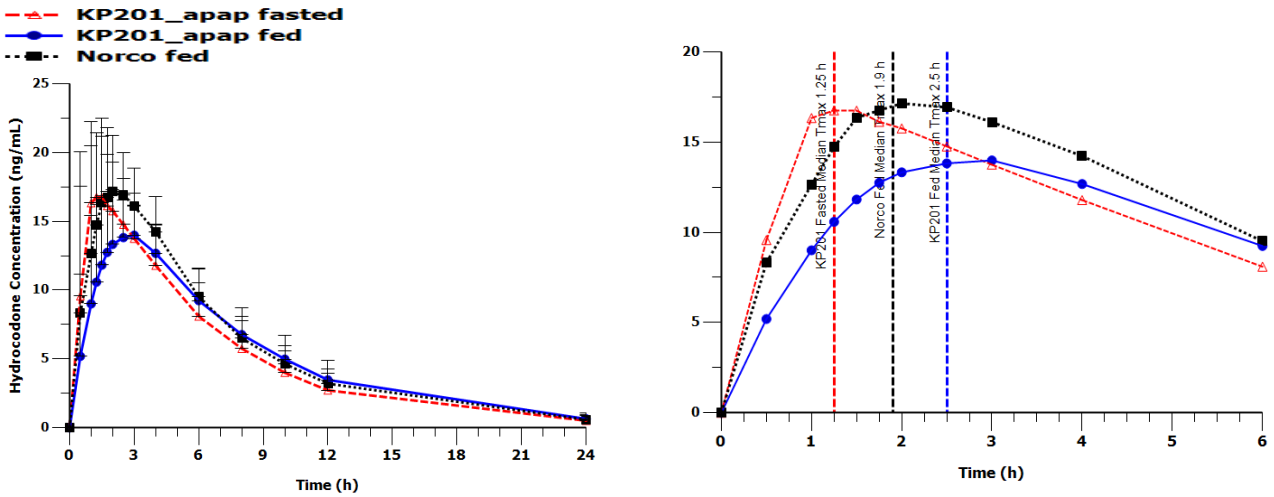
[a] Least squares geometric means, based on the analysis of natural log-transformed data.

Study KP201.104 evaluated the effect of food on the pharmacokinetics and relative bioavailability and of hydrocodone and acetaminophen from KP201/acetaminophen and Norco under fed conditions in healthy volunteers. The three treatment groups were:

- Treatment A: KP201/acetaminophen, 1 x 6.67 mg/325 mg tablet with 240 mL of water under fed conditions
- Treatment B: KP201/acetaminophen, 1 x 6.67 mg/325 mg tablet with 240 mL of water under fasted conditions.
- Treatment C: Norco Tablets, 1 x 7.5 mg/325 mg tablet under fed conditions

The results for the effects on plasma hydrocodone concentration over time for the 0 to 24 hour and 0 to 6 hour periods are provided in the following figure from Dr. Naraharisetti's review.

Figure 2: Study KP201.104 - Mean plasma hydrocodone concentration-time profile for 0-24h (left) and 0-6h (right).



The pharmacokinetic parameters for hydrocodone are summarized in the following tables.

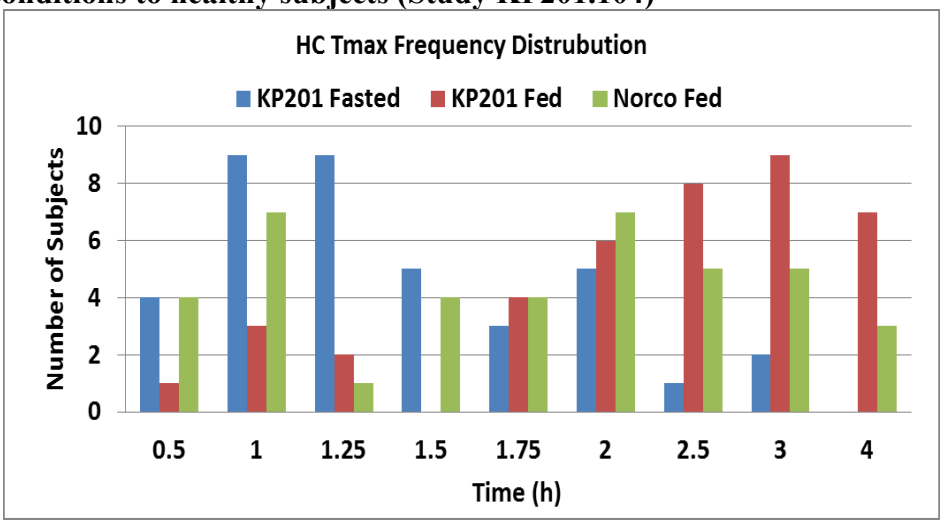
Table 3: Study KP201.104: Summary of pharmacokinetic parameters for hydrocodone, single-dose, fed and fasted conditions

Parameter [a]	KP201/APAP 6.67 mg/325 mg		Norco 7.5 mg/325 mg
	Fed	Fasted	Fed
Cmax (ng/mL)	16.04 ± 3.60	19.18 ± 4.84	20.95 ± 7.65
Tmax (h)	2.50 [0.50–4.00]	1.25 [0.50–3.00]	1.90 [0.50–4.00]
AUC0-t (h×ng/mL)	125.80 ± 26.90	121.40 ± 35.18	135.37 ± 30.30
AUCinf (h×ng/mL)	130.91 ± 29.45	125.73 ± 36.78	140.17 ± 31.66
t½ (h)	4.53 ± 0.70	4.33 ± 0.67	4.36 ± 0.68

[a] Arithmetic mean ± standard deviation except T_{max} for which the median. [Range] is reported.

As described in Dr. Naraharisetti's review, the comparison of hydrocodone C_{max} and AUC is similar to Norco under fed condition with a delay in the T_{max} of hydrocodone from KP201/ acetaminophen from a mean of 1.25 hours to a mean of 2.5 hours. Review of the individual T_{max} values found that there were no individuals with a delay in onset beyond the dosing interval of four hours. A frequency histogram for the T_{max} of hydrocodone from KP201/acetaminophen and Norco is presented in Figure 6. This is an important parameter for review, as some immediate-release abuse-deterrent formulations have demonstrated substantial delays in the onset of absorption of drug in the fed state (as discussed in the September 10, 2015, advisory committee meeting for NDA 206830, Avridi).

Figure 3: Frequency histogram for hydrocodone T_{max} following administration of single doses of KP201/acetaminophen under fasted and fed conditions and Norco under fed conditions to healthy subjects (Study KP201.104)

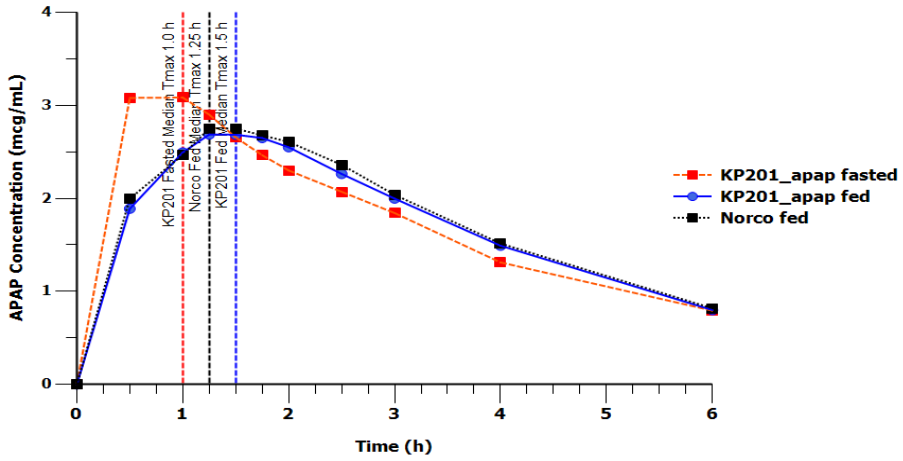


Dosing KP201/acetaminophen and Norco in the fed state led to median hydrocodone T_{max} values of 2.5 and 1.9 hours, respectively. The T_{max} ranges were identical and within the minimum recommended dosing interval of 4 hours (0.5 to 4 hours for both products). While

the hydrocodone C_{max} for KP201/acetaminophen under fed condition is 78% compared to Norco, the overall exposure to hydrocodone (AUC_{last} and AUC_{inf}) was within the 80% to 125% range. When hydrocodone partial AUCs in a typical dosing interval (4 to 6 hours) were compared for KP201/acetaminophen fed and Norco fed, the data demonstrated a slight decrease in hydrocodone partial exposure for KP201/acetaminophen compared to Norco. However, numerically it is not much lower and the standard deviations in hydrocodone partial AUCs overlapped between the two treatments.

The mean plasma acetaminophen concentration-time profile over a typical dosing regimen, (every 6 hours) with median T_{max} representation for KP201/acetaminophen under fasted and fed conditions and Norco under fed conditions is presented in Figure 9 and shows that there is little difference between KP201 and Norco for acetaminophen T_{max}, $C_{max,}$ and AUC in the fed state.

Figure 4: Mean plasma acetaminophen concentration-time profile (0-6h) following administration of single dose of KP201/acetaminophen under fasted and fed conditions and Norco under fed conditions to healthy subjects (Study KP201.104)



As noted by Dr. Naraharisetti, a there was a small delay in T_{max} for both hydrocodone and acetaminophen from KP201 under fed conditions compared to fasted conditions, the pharmacokinetic profiles and parameters under the fed condition are similar to those of Norco under the fed condition and the data support dosing without regard to the timing of food.

The multiple-dose pharmacokinetics of KP201, hydrocodone, and acetaminophen following a single dose on Day 1, and following multiple dosing as two tablets every four hours under fasted conditions were evaluated in Study KP201.03. The results are summarized in the following two tables from Dr. Naraharisetti's review.

Table 4: Study KP201.103: Single-dose and Multiple-dose pharmacokinetic parameters for hydrocodone

Parameter [a]	Single dose, Day 1 PK	Multiple dose, Q4H × 13 doses (Days 2 to 4), Day 4 PK
Cmax (ng/mL)	33.95 ± 8.41 (24)	62.79 ± 14.75 (24)
Tmax (h)	1.00 (24) [0.50–4.00]	1.25 (24) [0.50–2.00]
AUC0-4h (h×ng/mL)	92.94 ± 20.16 (24)	195.07 ± 47.66 (24)
AUCinf (h×ng/mL)	219.36 ± 57.28 (24)	-
t½ (h)	4.45 ± 0.59 (24)	4.87 ± 0.63 (24)

[a] Arithmetic mean ± standard deviation (N) except T_{max} for which the median (N) [Range] is reported.

Table 5: Study KP201.103: Single-dose and Multiple-dose pharmacokinetic parameters for acetaminophen

Parameter [a]	Single dose, Day 1 PK	Multiple dose, Q4H × 13 doses (Days 2 to 4), Day 4 PK
Cmax (µg/mL)	7.95 ± 2.16 (24)	11.0 ± 2.34 (24)
Tmax (h)	0.50 (24) [0.50–3.00]	1.00 (24) [0.50–1.50]
AUC0-4h (h×µg/mL)	17.6 ± 4.25 (24)	29.8 ± 6.19 (24)
AUCinf (h×µg/mL)	28.9 ± 7.07 (23)	-
t½ (h)	4.79 ± 1.21 (23)	6.84 ± 2.42 (23)

[a] Arithmetic mean ± standard deviation (N) except T_{max} for which the median (N) [Range] is reported.

Steady-state was reached for hydrocodone approximately 24 hours after the initiation of multiple dosing. The accumulation of hydrocodone for C_{max}, AUC_{0-4}, and AUC_{0-t} values (Day 4/Day1 or 14th dose/ 1st dose of KP201/acetaminophen) were 1.85-fold, 2.10-fold, and 2.03-fold, respectively.

Steady-state for acetaminophen was reached approximately between 24 and 36 hours after the initiation of multiple dosing. The accumulation of Cmax, AUC0-4, and AUC0-t values (Day 4/Day1 or 14th dose/ 1st dose of KP201/acetaminophen) were 1.38-fold, 1.69-fold, and 1.80-fold, respectively.

I concur with the conclusions reached by the clinical pharmacology reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

This section is not applicable to this application.

7. Clinical/Statistical: Efficacy

No new efficacy data were submitted for review during the second cycle. The following is from my first cycle review:

Support for the clinical efficacy of the benzhydrocodone and acetaminophen in Apadaz is based in part on reliance on the Agency's previous findings for the referenced drugs, Vicoprofen, a product containing hydrocodone and ibuprofen, and Ultracet, a product containing tramadol and acetaminophen. The Applicant conducted relative bioavailability studies as the scientific bridge for doing so. In addition, the Applicant has demonstrated bioequivalence to the hydrocodone and acetaminophen in Norco, a marketed product containing hydrocodone and acetaminophen, providing support that the exposure to hydrocodone and acetaminophen from Apadaz is consistent with an approved product and demonstrates that the combination is not novel and does not require factorial design efficacy studies as described in 21 CFR 300.50. No additional efficacy data are needed.

8. Safety

No new safety data were submitted for review during the second cycle. The following is from my first cycle review:

The primary support for the safety of Apadaz is based on the Agency's prior findings of safety for hydrocodone and acetaminophen. No additional data were required to assess the clinical safety of the benzhydrocodone because the prodrug was not present in the blood after oral dosing in humans long enough for detection. This supports the Applicant's contention that benzhydrocodone is rapidly hydrolyzed to hydrocodone. Safety data were collected during the pharmacokinetic and human abuse liability studies. A total of 418 healthy subjects received at least one dose of KP201/acetaminophen and 245 healthy subjects received multiple doses of KP201/acetaminophen across ten clinical studies. Twenty-six of the subjects were pre-treated with naltrexone during Study KP201.103. There were no deaths or serious adverse events. Seven patients discontinued study participation due to adverse events. Four of these patients experienced hypotension including one with presyncope, two nausea and vomiting, and one supraventricular and ventricular extrasystoles. The hypotension and nausea and vomiting were likely related to study drug and all resolved spontaneously. The one patient with the supraventricular and ventricular extrasystoles had no history of cardiac disease, but was found to have left ventricular hypertrophy at baseline and on follow up electrocardiogram with premature ventricular complexes on ECG three weeks after study discontinuation. The findings are unlikely related to study participation.

The most common adverse events reported were constipation, nausea, somnolence, fatigue, headache and dizziness. Overall, the safety data indicate that Apadaz has a similar safety profile to existing hydrocodone/acetaminophen formulations and no new safety concerns were identified with this product.

9. Advisory Committee Meeting

The following is from my first cycle review.

This application was taken to a joint meeting of the Anesthesia and Analgesia Drug Advisory Committee and the Drug Safety and Risk Management Advisory Committee on May 5, 2016. The discussion points for the committees were focused on two areas, whether the nasal route of abuse is relevant for hydrocodone and acetaminophen combination products and whether the studies conducted by the Applicant demonstrated properties likely to deter abuse.

The following is a summary of the discussion and voting questions from the advisory committee meeting.

Question #1
Discuss whether the data presented for hydrocodone and acetaminophen combination drug products support that the nasal route of abuse is relevant for KP201/acetaminophen?

The overall consensus of the committees was that while the nasal route of abuse is less common than the oral route, it may be relevant for hydrocodone/acetaminophen products and Apadaz, even if there is only a small amount of abuse occurs by this route. The committee noted that this route may be more relevant in certain communities and age groups, such as adolescents, based on the data presented.

Question #2
Please discuss whether there are sufficient data to support a finding that KP201/acetaminophen has properties that can be expected to deter abuse for each of these possible routes of abuse:

a. Oral
b. Nasal
c. IV

The general consensus of the committees was that the data did not support a finding that Apadaz was likely to deter abuse by the oral or intranasal routes of abuse, nor was the in vitro data supportive of an advantage in resistance to separation of the acetaminophen from the opioid.

Question #3
Should KP201/acetaminophen be approved for the proposed indication?

The committees voted 16 to 4 in favor of approving Apadaz for the proposed indication, noting that there was bioequivalence of hydrocodone and acetaminophen to the comparators and it would be likely be effective for the proposed indication without any greater safety risk for patients. The four committee members who voted against approval commented that they did not find the product to be any safer than currently available therapies. One committee member voted against approval because of the lack of abuse-deterrent properties.

Question #4
If approved, should KP201/acetaminophen be labeled as an abuse-deterrent product?

The committees voted 18 to 2 against labeling Apadaz with abuse-deterrent language. The

committees expressed concern that the data presented did not support a finding of abuse-deterrent properties and were concerned that labeling the product as abuse-deterrent would misguide prescribers into thinking that it may be safer, and would potentially undermine the standard for labeling products as abuse-deterrent properties. The two committee members who voted to label Apadaz with abuse-deterrent language stated that they thought the data supported an incremental improvement over currently available therapies.

10. Pediatrics

As Apadaz contains a novel drug substance, the product is subject to the requirements of the Pediatric Research Equity Act (PREA). The Applicant reached agreement with the Division on an Initial Pediatric Study Plan (IPSP) on October 13, 2015. The proposed IPSP was discussed at the Pediatric Review Committee (PeRC) meeting on May 4, 2016. There was consensus that a deferral was appropriate for all the following required studies because the product is ready for approval in adults:

1. Pharmacokinetic, safety, and efficacy study for ages birth to < 2
2. Open-label pharmacokinetic, safety and efficacy study for ages 2 to < 7
3. Open-label pharmacokinetic, safety and efficacy study for ages 7 to < 17

In addition, the Applicant agreed to conduct a juvenile animal study of benzhydrocodone to support pediatric studies in children from birth to 2 years of age.

11. Other Regulatory Issues

The following is from my first cycle review.

Evaluation of Abuse-Deterrent Properties

The Applicant conducted in vitro and in vivo studies to evaluate the abuse-deterrent properties of Apadaz. The clinical studies used for this assessment are very similar in design and conduct to the studies used to determine the abuse potential of a novel product. For the latter, the primary question is to determine the abuse liability, often as part of an assessment for scheduling under the Controlled Substances Act and the outcomes of Drug High and Drug Liking relative to a comparator with similar pharmacological properties. When used to evaluate possible abuse-deterrent properties, the primary question is whether the purported abuse-deterrent properties of the product will decrease the likelihood of abuse by any of the routes tested relative to either a non-abuse deterrent comparator of the same product, or another abuse-deterrent product. In this setting, the important outcomes include Drug Liking and Drug High, but more importantly, whether there is a difference in the subject's willingness to take the drug again relative to the comparator. Depending on the nature of the abuse-deterrent properties, the pattern of results of Take Drug Again, Drug Liking, and Drug High can differ substantially. For example, a product designed with aversive abuse-deterrent features may result in the same Drug High as a comparator, but the aversive properties may make the subject less willing to take the drug again,

while a product with physicochemical properties intended to prevent crushing or dissolution may result in lower scores for Drug Liking, Drug High, and Take Drug Again. For Apadaz, the Applicant expected to see a change in the pharmacokinetic profile of hydrocodone following insufflation of crushed tablets hypothesizing that there would be less or slower conversion to hydrocodone by the nasal route than by the oral route. As described in the review of the clinical abuse liability studies, there were no statistically significant differences in the responses to KP201/acetaminophen as compared to Norco, with a small numerical reduction in Drug High, but no difference in Drug Liking, and importantly, no difference in willingness to take the product again.

In Vitro Studies

The Applicant conducted studies to evaluate the solubility and extraction of benzhydrocodone from the tablet in large and small volume extraction studies using a range of solvents, pH buffers, temperature, and agitation. As noted in the chemistry review, additional testing conditions were requested and the Applicant submitted the results. Studies were also conducted to assess the potential of releasing (hydrolyzing) hydrocodone from KP201 under a range of conditions. Small volume extractability and syringeability studies were designed to assess the solubility profiles of KP201 and hydrocodone bitartrate in aqueous solutions of varying pH and salinity that bracket physiological conditions. Smokability was assessed using a "two-trap" system at the temperature just above which 90% of the API mass was lost during the TGA studies. Studies were carried out using hydrocodone free base, hydrocodone bitartrate, KP201 free base, KP201, the drug product, and the immediate-release comparator tablet. The details of the study designs and study variables can be found in the chemistry review.

The large volume extraction studies demonstrated that under certain conditions, the extraction behavior of KP201 diverges from hydrocodone bitartrate and hydrocodone. Under some conditions where the solubility of KP201 remains low, acetaminophen continued to partition into solution, possibly facilitating separation of the two drug substances. There were some hydrolyzing solvents that did yield hydrocodone from KP201. The small volume extraction studies showed that KP201 was generally less soluble than hydrocodone bitartrate/hydrocodone. The Apadaz formulation does not offer resistance to syringing and there were no differences from the comparator for syringeability or injectability. Neither product was suitable for smoking.

Clinical Studies

Three clinical studies were conducted to evaluate the abuse-deterrent properties of Apadaz. One oral abuse potential study and one intranasal abuse potential study were adequately designed and controlled studies of benzhydrocodone and acetaminophen compared with a generic formulation of hydrocodone and acetaminophen, Norco. A third intranasal study was not adequately designed to evaluate the abuse-deterrent properties of Apadaz, in part because the treatment groups did not include acetaminophen, but also due to problems with the study design.

Study KP201.A01 was a randomized, double-blind, placebo- and active-controlled, single-dose, seven-way crossover study that evaluated the relative bioavailability, abuse potential, and safety

of equivalent oral doses of KP201/acetaminophen compared to an immediate-release hydrocodone/acetaminophen tablet in opioid experienced, nondependent subjects. Subjects who completed a naloxone challenge without signs or symptoms of opioid withdrawal went on to the Drug Discrimination phase of the study to establish whether they could differentiate active drug from matching placebo using six over-encapsulated Norco tablets, 7.5 mg/325 mg, for a total of 45 mg or hydrocodone bitartrate and 1950 mg of acetaminophen. Subjects who demonstrated adequate separation of active drug from placebo were then randomized to the double-blind, randomized, seven-period crossover Treatment Phase. The study drugs were over-encapsulated for blinding, and 12 capsules were administered for each treatment.

The treatment groups were:

- 12 KP201/acetaminophen 6.67 mg/325 mg tablets
- 8 KP201/acetaminophen 6.67 mg/325 mg tablets with 4 placebo capsules
- 4 KP201/acetaminophen 6.67 mg/325 mg tablets with 8 placebo capsules
- 12 Norco 7.5/325 mg tablets
- 8 Norco 7.5/325 mg tablets with 4 placebo capsules
- 4 Norco 7.5/325 mg tablets with 8 placebo capsules
- 12 placebo capsules

The study outcomes were:

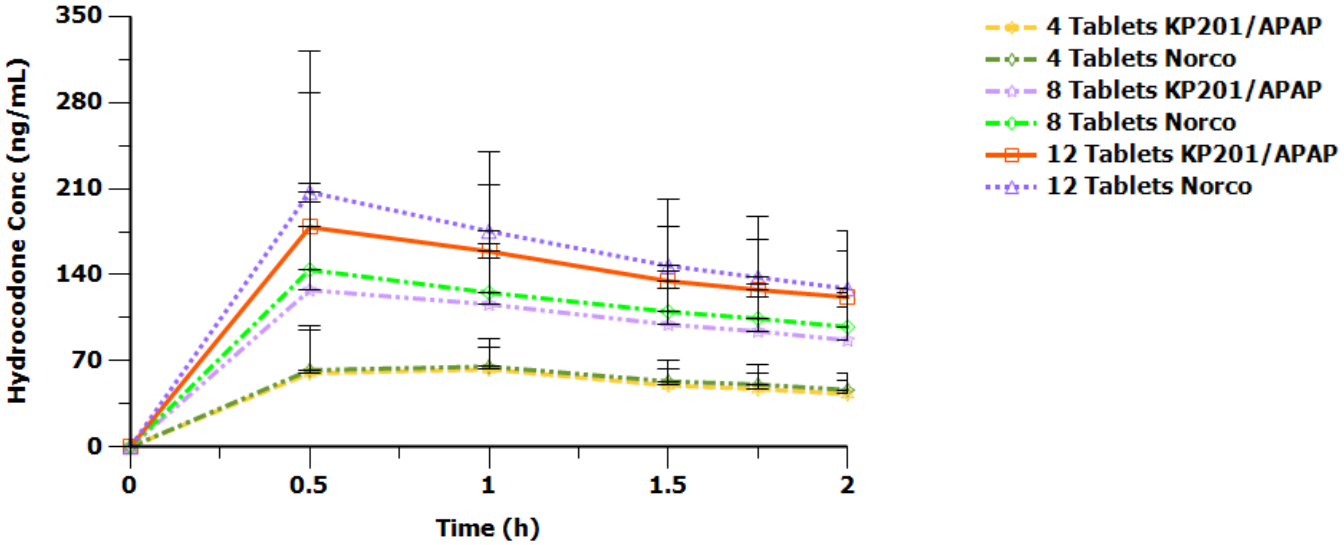
- Bipolar Drug Liking VAS
- Bipolar Take Drug Again VAS
- Bipolar Overall Drug Liking VAS
- Drug Effects Questionnaire consisting of unipolar VAS to assess any drug effects, good effects, bad effects, feeling high, feeling sick, nausea, feeling sleepy, and feeling dizzy.
- Addiction Research Center Inventory-Morphine-Benzedrine Group Subscale (ARCI-MBG)

Blood samples for pharmacokinetic analysis were taken pre-dose and at selected times for 24 hours following the dose.

Of the 151 subjects screened, 125 underwent the naloxone challenge, and 119 went on to the Drug Discrimination phase. Thirty-seven subjects failed to meet the criteria for drug discrimination and an additional 11 discontinued due to adverse events, positive urine drug screen, investigator decision, or withdrew consent. Sixty-two of the remaining 71 subjects completed the Treatment Phase.

The results of the pharmacokinetic analysis are shown in the following figure from Dr. Tolliver's review. There is a slightly lower hydrocodone level from the KP201/acetaminophen high dose group, but as shown below, this difference was not sufficient to have an effect on the pharmacodynamic outcomes.

Figure 5: Mean plasma hydrocodone concentration-time profiles following single oral doses of KP201/acetaminophen in opioid-experienced, non-dependent recreational users, Study KP201.A01



The results of the pharmacodynamic outcome measures showed a dose response, but no statistically significant differences between the active and comparator for Drug High, Drug Liking, or Take Drug Again. There were small numerically greater responses for Take Drug Again for KP201/acetaminophen. The summary statistics from Dr. Chen's review are provided below in a modified table.

Table 6: Summary statistics for Drug Liking, High, and Take Drug Again, E_{max} (N=62), Study KP201.A01

	TRT	Mean	SD	Min	Q1	Med	Q3	Max
Drug Liking	HB/APAP L	72.5	16.46	50	60	68.5	82.5	100
	HB/APAP M	83.4	16.41	50	71.75	86	100	100
	HB/APAP H	87.4	15.63	50	78.75	93	100	100
	KP201/APAP L	72.6	17.17	50	56.75	71.5	84	100
	KP201/APAP M	82.4	16.42	50	69.25	83	100	100
	KP201/APAP H	87.8	14.78	50	77.75	94	100	100
	P	51.5	3.38	50	50	51	51	69
High Effects	HB/APAP L	48.2	30.79	0	21.5	49	72.25	100
	HB/APAP M	76.6	25.84	4	62	83.5	100	100
	HB/APAP H	85.1	21.68	0	76	97	100	100
	KP201/APAP L	49.6	32.98	0	16.5	56.5	72.25	100
	KP201/APAP M	72.6	25.06	4	57.25	77	96	100
	KP201/APAP H	85.5	19.32	9	76.5	95	100	100
	P	2.6	9.79	0	0	0	1	67
Take Drug Again	HB/APAP L	66.3	20.65	37	49	52	84.5	100
	HB/APAP M	66.0	28.30	0	49	66.5	94	100
	HB/APAP H	66.5	25.51	0	49	63	94.5	100
	KP201/APAP L	69.3	22.48	11	49	65	91.5	100
	KP201/APAP M	71.5	23.28	0	49	73	93	100
	KP201/APAP H	72.4	24.44	0	49.75	75.5	100	100
	P	49.6	9.86	1	49	49	50	99

Study KP201.A02 was a randomized, double-blind, placebo- and active-controlled, single-dose, seven-way crossover study that evaluated the relative bioavailability, abuse potential, and safety of equivalent intranasal doses of KP201/acetaminophen compared to an immediate-release hydrocodone/acetaminophen tablet in opioid experienced, nondependent subjects, with a history of intranasal abuse of opioids. Subjects who completed a naloxone challenge without signs or symptoms of opioid withdrawal went on to participate further in the study. Part A of the study was used for dose selection. After successful completion of the Qualification Phase in which subjects adequately distinguished 40 mg of hydrocodone bitartrate from placebo, subjects were assigned to receive either KP201/acetaminophen or Norco and a matching placebo. Cohorts of four subjects evaluated doses up to four crushed tablets of KP201/acetaminophen and Norco.

The Part B treatment groups were:

Treatment	Intranasal Dose	Oral Dose with 240 mL Water
A	**Placebo Powder** (975 mg Microcrystalline Cellulose Powder)	**Placebo** (2 over-encapsulated lactose tablets)
B	**Placebo Powder** (975 mg Microcrystalline Cellulose Powder)	**KP201/APAP (13.34 mg/650 mg)** (2 over-encapsulated tablets)
C	**KP201/APAP (13.34/650 mg)** (2 Crushed Tablets) (1100 mg Powder)	**Placebo** (2 over-encapsulated lactose tablets)
D	**Norco (15 mg/650 mg)** (2 crushed Norco Tablets) (850 mg Powder)	**Placebo** (2 over-encapsulated lactose tablets)
E	**Placebo Powder** (975 mg Microcrystalline Cellulose Powder)	**Norco (15 mg/650mg)** (2 over-encapsulated tablets)

As noted by Dr. Tolliver, "Intranasal treatments were prepared by crushing KP201/acetaminophen and Norco tablets for 2 minutes using a mortar and pestle. Subjects were instructed to insufflate the IN treatment within 10 minutes. Subjects were not allowed to blow their nose for at least two hours post-dose, and any episodes of sneezing within two hours post-dose were documented. Start and stop times for intranasal administration were recorded and the amount (%) of study drug not insufflated was recorded. Any difficulties, problems, and adverse effects during insufflation and their cause(s) were also documented."

The dose selected for Part B was two tablets. The reasons for this selection were summarized by Dr. Tolliver:

> "Treatment with 2 Tablets of KP201/acetaminophen and Norco – Selected for Main Study (Part B)
> - Six out of 7 subjects (cohorts 1W and 2 W combined) displayed a greater than 15 mm difference for E_{max} of Drug Liking between KP201/acetaminophen and placebo.
> - Five out of 8 subjects (cohorts 1X and 2X combined) displayed a greater than 15 mm difference for E_{max} of Drug Liking between Norco and placebo.
> - All 7 subjects (cohorts 1W and 2 W combined) completely insufflated the dose of KP201/acetaminophen and indicated insufflation was easy rather than difficult based on Ease of Snorting scores.
> - Six out of 8 subjects were able to insufflate greater than 95% of the Norco dose and considered insufflation easy based on Ease of Insufflation VAS. Two remaining subjects noted insufflation was difficult, insufflating 67.3% and 55.4% of the HB/acetaminophen dose.
>
> The three-tablet dose was not considered for evaluation in Part B because in Cohort 6X (4 subjects, only cohort used) the active control (HB/acetaminophen) did not produce reliable significant Drug Liking effects at this dose level. In only 1 of the 4 subjects, was there a greater (i.e., 76 mm vs 51 mm) than 15 mm for E_{max} of Drug Liking between Norco and placebo.
>
> Due to the intranasal irritation observed at the highest dose tested (i.e., four-tablet dose) for both KP201/APAP and Norco, with KP201/APAP producing overall higher scores on

the Likert scale and adverse nasal effects compared to Norco, the Sponsor concluded that a four-tablet dose administered intranasally would not have been well tolerated in the Main Study (Part B)."

The study outcomes were:

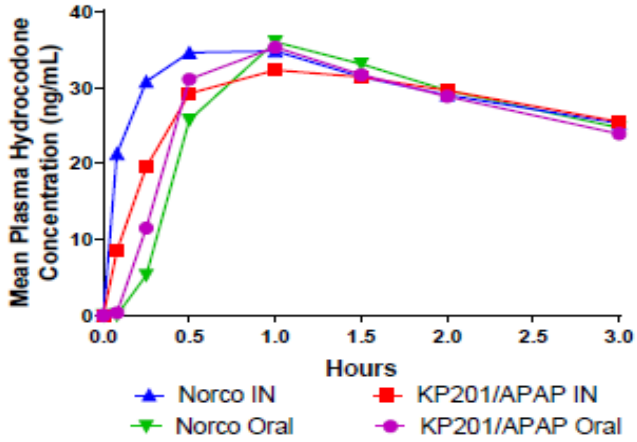
- Bipolar Drug Liking VAS
- Bipolar Take Drug Again VAS
- Bipolar Overall Drug Liking VAS
- Drug Effects Questionnaire consisting of unipolar VAS to assess any drug effects, good effects, bad effects, feeling high, feeling sick, nausea, feeling sleepy, and feeling dizzy.
- Addiction Research Center Inventory-Morphine-Benzedrine Group Subscale (ARCI-MBG)

Blood samples for pharmacokinetic analysis were taken pre-dose and at selected times for 24 hours following the dose.

Part B enrolled 71 subjects who successfully completed a naloxone challenge test. Twenty-three of these subjects failed the Drug Discrimination Test and two subjects withdrew consent, leaving 46 subjects eligible for the Treatment Phase of Part B. Forty-two subjects completed the Treatment Phase. One subject was withdrawn in following adverse events of mild supraventricular and ventricular extrasystoles that resolved on the same day as onset and one subject was lost to follow-up after completing Treatment Period 1. Two subjects were withdrawn after completing Treatment Period 1 because the sponsor decided to stop enrollment after 40 subjects had completed all 5 treatment periods in accordance with the protocol.

The results of the pharmacokinetic analysis are shown in the following figure from Dr. Tolliver's review. The earliest exposure to hydrocodone was from the intranasal Norco group, followed by intranasal KP201/acetaminophen, oral KP201/acetaminophen , and then oral Norco. C_{max} levels were similar across all four groups.

Figure 6. Plasma Hydrocodone Concentrations as a Function of Time Following Oral and Intranasal Treatments with KP201/acetaminophen (13.34 mg/650 mg) and Norco (15 mg/650 mg) (N=43 Subjects for Intranasal Treatments and 42 for Oral Treatments) Study KP201.A02)



The pharmacokinetic data were somewhat surprising in that the exposure to hydrocodone following insufflation of KP201/acetaminophen was comparable to oral ingestion of KP201/acetaminophen and Norco, and only slightly delayed compared to insufflation of Norco. This suggests that either conversion of KP201 in the blood occurs nearly as quickly in the GI tract, or most of the insufflated powder was swallowed and effectively mimicked oral ingestion.

The following table from Dr. Tolliver's review shows the pharmacodynamic endpoint results. There were no statistically significant differences for Drug Liking, Drug High, or Take Drug Again when comparing intranasal KP201/acetaminophen and Norco administered orally or administered nasally. These findings were not surprising given the results of the pharmacokinetic data.

Table 7. Descriptive Statistics for Drug Liking VAS, High VAS, and Take Drug Again VAS Oral and Intranasal Administration of Norco (15 mg/650 mg) and KP201/acetaminophen (13.34/650 mg). (Completer Population = 42 Subjects) KP201.A02

VAS	Treatment	Mean Emax	Standard Deviation	Minimum	1st Quadrile	Median	3rd Quadrile	Maximum
Bipolar Drug Liking	Crushed Norco IN	79.0	17.59	50	64.75	80	100	100
	Intact Norco Oral	77.9	16.71	50	64.75	74.5	99.25	100
	Crushed KP201/APAP IN	75.9	15.08	50	64.5	74	88.25	100
	Intact KP201/APAP Oral	76.9	17.28	50	63.5	76	93.25	100
	Placebo	53.0	7.68	50	50	51	51	85
Unipolar High	Crushed Norco IN	59.1	32.74	0	28.75	67.5	85.25	100
	Intact Norco Oral	60.3	31.54	0	33.75	69	84.5	100
	Crushed KP201/APAP IN	61.8	30.13	0	39	68.5	84	100
	Intact KP201/APAP Oral	61.2	33.24	0	32.75	70	88	100
	Placebo	8.8	24.56	0	0	0	3	100
Bipolar Take Drug Again	Crushed Norco IN	74.5	25.54	0	55	81.5	100	100
	Intact Norco Oral	75.6	23.59	0	61.75	75	100	100
	Crushed KP201/APAP IN	69.5	25.11	0	52.5	68	97	100
	Intact KP201/APAP Oral	73.3	26.46	0	51	78.5	100	100
	Placebo	48.2	14.55	0	50	50	51	100

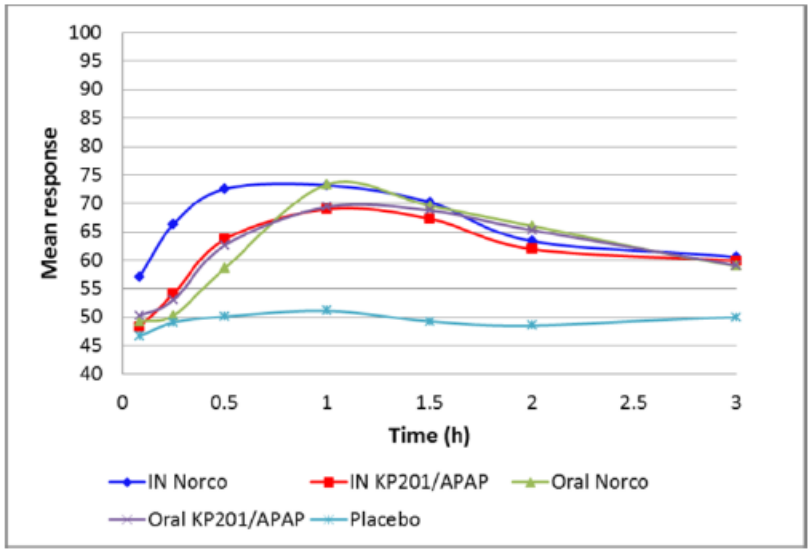
Study KP201.A03 was not designed properly to evaluate the abuse-deterrent characteristics of KP201/acetaminophen relative to Norco. As noted by Dr. Tolliver, "Study KP201.A03 was originally designed as a pharmacokinetic/nasal tolerability study to which was added an assessment for Drug Liking VAS. This study was conducted on the active pharmaceutical ingredients (API), namely KP201 and hydrocodone bitartrate, and not on the products KP201/acetaminophen and hydrocodone bitartrate/acetaminophen (Norco). There was no placebo treatment arm and therefore, no validation of the Drug Liking VAS. There was no Drug Discrimination Phase in this study. As such it is not known to what extent subjects were able to discriminate active treatments (KP201 API (13.34 mg) and hydrocodone bitartrate API (15.00 mg)) from a placebo with regard to Drug Liking VAS." This study will not be considered further.

Overall, the results of the in vitro and clinical abuse potential studies do not demonstrate any differentiation of Apadaz from the non-abuse-deterrent hydrocodone/acetaminophen product. These data do not support a finding that Apadaz can be expected to reduce abuse by any route of administration.

New to second cycle review:

Throughout the FDRRs and for this second review cycle, the Applicant has disagreed with the agency reviewer's analyses of the abuse-deterrent study data, particularly the results of the intranasal human abuse potential study. The primary area of disagreement has been whether the standard applied to other products, as described in the guidance for industry, is appropriate for this product, or if a different standard is more appropriate. The former relies on an analysis of maximum effect (Emax) for the pharmacodynamic endpoints of Drug High, Drug Liking, and Take Drug Again. The latter standard argued by the Applicant is to rely on area under the curve analyses of drug liking during the first 0.5 hours, one hour and two hours which correlate with small differences in hydrocodone exposure for Apadaz as compared to Norco. The differences in hydrocodone levels were small, as demonstrated in Figure 5 above, as were the differences in the early results of the pharmacodynamic endpoints presented in the following figure from Dr. Tolliver's first cycle review. In Figure 6, while there is a shift later for the initial rise of the drug liking for Apadaz by oral and nasal routes, relative to nasal Norco, oral Norco was the latest and slowest to rise of all treatment groups.

Figure 6. Mean Time Course profile for Drug Liking Following Intranasal and Oral Administration of KP201/APAP (Apadaz) (13.34 mg/650 mg) and Norco (15 mg/650 mg). (Source: CDER Office of Biostatistics)



Given the lack of difference in the maximum Drug Liking, Drug High and Take Drug Again endpoints, it is inappropriate to overly weight these small early differences.

Risk Mitigation

The following is from a REMS memo by Dr. Judith Racoosin.

> In September 2017, after consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, the determination was made that a REMS is necessary to ensure that the benefits of the class of IR opioid analgesic products that are intended for use in the outpatient setting outweigh the risks of adverse outcomes of

addiction, unintentional overdose, and death resulting from inappropriate prescribing, abuse, and misuse. The IR opioid analgesic products in this class contain one of the following active drug substances: morphine, codeine, dihydrocodeine, pentazocine, oxycodone, hydrocodone, fentanyl, buprenorphine, methadone, hydromorphone, oxymorphone, tramadol, or tapentadol; none of these active drug substances are new molecular entities. On September 28, 2017, REMS notification letters were issued to the sponsors of IR opioid analgesic products that are intended for use in the outpatient setting. On the same date, REMS modification letters were issued to the sponsors of extended-release and long-acting opioid analgesics to encompass the IR products.

Consequently, after additional consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, the determination has been made that until the class-wide REMS for all opioid analgesic products intended for outpatient use is established, a REMS that includes a Medication Guide and a Communication Plan is necessary to ensure that the benefits of APADAZ (benzhydrocodone and acetaminophen) outweigh the risks of adverse outcomes of addiction, unintentional overdose, and death resulting from inappropriate prescribing, abuse, and misuse.[5]

KemPharm has submitted a REMS that has been reviewed by the Office of Surveillance and Epidemiology. The elements of the REMS will be a Medication Guide, a Communication Plan, and a timetable for submission of assessments of the REMS. Development of the shared system opioid analgesic REMS is currently underway. Once approved, KemPharm will be required to submit a modified REMS consistent with the shared system opioid analgesic REMS; it is anticipated that APADAZ will become a member of that REMS.

12. Labeling

Labeling reviews were conducted by the Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis. Recommended changes were incorporated. The proprietary name, Apadaz, was reviewed and found acceptable.

During the first cycle, the Division of Pediatric and Maternal Health provided recommendations for sections 8.1, 8.2, 8.3 and 17 of the prescribing information to make the labeling compliant with the Pregnancy and Lactation Labeling Rule and to be consistent with other opioid and acetaminophen products indicated for short-term management of acute pain.

The Applicant has proposed the following language for section 9.2 to describe the results of the intranasal human abuse potential study:

Intranasal Clinical Abuse Potential Study[54]

In an intranasal single-center, randomized, double-blind, double-dummy, two-part human abuse potential study, 46 recreational opioid users were randomized into the Treatment Phase; 42

[5] When the opioid analgesic class REMS is approved, it is anticipated that APADAZ will become a member of that shared system REMS.

subjects completed the study. Five treatment arms included intranasal crushed and oral APADAZ (2 tablets, each containing 6.12 mg benzhydrocodone and 325 mg acetaminophen), intranasal crushed and oral hydrocodone/acetaminophen (2 tablets, each containing 4.54 mg hydrocodone and 325 mg acetaminophen, and intranasal placebo powder. The respective dosage strengths for APADAZ and hydrocodone/acetaminophen contained equimolar amounts of hydrocodone.

The following is the final agreed upon language for section 9.2:

In an intranasal single-center, randomized, double-blind, double-dummy, two-part human abuse potential study, 46 recreational opioid users were randomized into the Treatment Phase; 42 subjects completed the study. Five treatment arms included intranasal crushed and oral APADAZ (2 tablets, each containing 6.12 mg benzhydrocodone and 325 mg acetaminophen), intranasal crushed and oral hydrocodone/acetaminophen (2 tablets, each containing 4.54 mg hydrocodone and 325 mg acetaminophen), and intranasal placebo powder. The respective dosage strengths for APADAZ and hydrocodone/acetaminophen contained equimolar amounts of hydrocodone.

The pharmacokinetic data showed that overall (AUC_{last}, AUC_{inf}, and C_{max}) hydrocodone exposure was comparable between intranasal crushed APADAZ and intranasal crushed hydrocodone/acetaminophen. These treatments were also comparable with cumulative hydrocodone exposure at the timepoints of 4, 8, and 24 hours (AUC_{0-4}, AUC_{0-8}, AUC_{0-24}). Over the first 2 hours post-dosing ($AUC_{0-0.5}$, AUC_{0-1}, and AUC_{0-2}), the cumulative hydrocodone exposure was lower following intranasal APADAZ compared to intranasal hydrocodone/ acetaminophen.

There were numerically small but not statistically significant differences between APADAZ and the hydrocodone-acetaminophen control observed for the pre-specified primary endpoint, maximum effect on Drug Liking VAS (E_{max}), and the secondary endpoints of E_{max} for High VAS and Take Drug Again VAS.

Table 2: Summary Statistics of Maximum Scores (E_{max}) on Drug Liking, High and Take Drug Again, Following Intranasal Administration of Apadaz, Hydrocodone/APAP, and Placebo

VAS Scale (100 point) *intranasal (n=42)*	Apadaz Crushed	Hydrocodone/APAP Crushed	Placebo
Drug Liking *			
Mean (SE)	75.9 (2.3)	79.0 (2.7)	53.0 (1.2)
Median (Range)	74.0 (50-100)	80.0 (50-100)	51.0 (50-85)
High**			
Mean (SE)	61.8 (4.6)	59.1 (5.1)	8.8 (3.8)
Median (Range)	68.5 (0-100)	67.5 (0-100)	0.0 (0-100)
Take Drug Again*			
Mean (SE)	69.5 (3.9)	74.5 (3.9)	48.2 (2.2)
Median (Range)	68.0 (0-100)	81.5 (0-100)	50.0 (0-100)

*Bipolar scale (0=maximum negative response, 50=neutral response, 100=maximum positive response)

** Unipolar scale (0=maximum negative response, 100=maximum positive response)

Additional secondary analyses of Drug Liking based on area under the effect curve analyses (AUE) for the first half hour, hour, and 2 hours post-dosing, demonstrated numerically small differences between intranasal APADAZ and intranasal hydrocodone/acetaminophen. However, there were no differences between these two treatments with respect to the cumulative High experienced over the first 2 hours post-dosing using similar AUE analyses. There are no data to support that small differences in the early Drug Liking experience over the first 2 hours are clinically relevant findings consistent with possible abuse-deterrent effects, particularly in the setting of the E_{max} analyses for Drug Liking, Take Drug Again, and High that do not support a deterrent effect. Based on the overall results, APADAZ cannot be expected to deter abuse by the intranasal route of administration.

Summary
The in vitro studies that evaluated physical manipulation and extraction for the purpose of preparing APADAZ for abuse by the intravenous route or by smoking did not find an advantage for APADAZ over the hydrocodone/acetaminophen control.

The results of the oral and intranasal human abuse potential studies do not support a finding that APADAZ can be expected to deter abuse by the oral or nasal routes of administration.

The indication will be as follows:

Apadaz is indicated for the short-term (no more than 14 days) management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

Limitations of Use
Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, reserve APADAZ for use in patients for whom alternative treatment options [e.g., non-opioid analgesics]:

- Have not been tolerated, or are not expected to be tolerated,
- Have not provided adequate analgesia, or are not expected to provide adequate analgesia

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action – Approval

- Risk Benefit Assessment

Apadaz can be expected to perform as an analgesic comparably to Norco (hydrocodone/acetaminophen) when dosed to provide comparable amounts of hydrocodone and acetaminophen. Although the purpose of creating benzhydrocodone was to impart abuse-deterrent properties to the product, both in vitro and in vivo testing failed to demonstrate any meaningful differences from Norco. The Applicant has agreed to labeling that describes a lack of meaningful difference from Norco in the description of abuse-deterrent studies in section 9.2 of the package insert.

- Recommendation for Postmarketing Risk Management Activities

Apadaz has a REMS with the elements of a Medication Guide, a Communication Plan, and a timetable for submission of assessments of the REMS. Development of the shared system opioid analgesic REMS is currently underway. Once approved, KemPharm will be required to submit a modified REMS consistent with the shared system opioid analgesic REMS; it is anticipated that Apadaz will become a member of that REMS.

- Recommendation for other Postmarketing Study Commitments

3037-1 An open-label PK and safety study in ages 7 to less than 17 years of age.

3037-2 An open-label PK and safety study in ages 2 to less than 7 years of age.

3037-3 A PK, safety, and efficacy study in ages 0 to less than 2 years of age.

3037-4 Conduct a juvenile animal toxicology study in the rat with benzhydrocodone to support dosing of APADAZ in children ≤ 2 years of age.

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/s/

SHARON H HERTZ
02/23/2018