CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209777Orig1s000

MEDICAL REVIEW(S)

Combined Cross-Discipline Team Leader Review and Clinical Review

Date	(electronic stamp)
From	Anjelina Pokrovnichka, MD and Joshua Lloyd, MD
Subject	Combined Cross-Discipline Team Leader Review and Clinical Review
NDA#	209777
Applicant	Inspirion Delivery Sciences, LLC
Date of Submission	October 21, 2016
PDUFA Goal Date	April 21, 2017
Proprietary Name / Established (USAN) names	RoxyBond / Oxycodone hydrochloride
Dosage forms / Strength	Oral tablets / 5 mg, 15 mg, and 30 mg
Proposed Indication(s)	Management of moderate to severe pain where the use of an opioid analgesic is appropriate.
Recommended:	Approval

1. Introduction

Inspirion Delivery Sciences, LLC ("Applicant") submitted a new drug application (NDA) under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for RoxyBond (oxycodone hydrochloride) tablets, an immediate-release (IR) formulation of oxycodone with properties intended to deter abuse by the intranasal and intravenous routes of administration. This NDA relies on the agency's prior findings of safety and effectiveness for Roxicodone (NDA 021011; approved August 31, 2000), which is a non-abuse-deterrent IR formulation of oxycodone approved for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. The Applicant developed RoxyBond under IND 105,951 under the name abuse-resistant, immediate-release oxycodone (Oxycodone ARIR) tablets and proposes to market 5, 15, and 30 mg strengths.

The Applicant requested and was granted priority review (6-month review clock) status, as there are no IR oxycodone products, or IR opioid products in general, approved with abuse-deterrent labeling consistent with FDA's abuse-deterrent opioid guidance document[1] published April 2015.

Efficacy and safety studies were not conducted with or required for RoxyBond, as the safety and effectiveness of RoxyBond are supported by relative bioavailability data (Study O-ARIR-003) to bridge to the agency's previous findings for the referenced drug. The Applicant conducted an additional dose-proportionality pharmacokinetic (PK) study (Study O-ARIR-006) to support marketing all of the proposed tablet strengths.

[1] https://www.fda.gov/downloads/Drugs/Guidances/UCM334743.pdf, accessed 4/11/17

This review will specifically focus on the clinical aspect of the pharmacokinetic study results as well as the in vitro and in vivo data intended to support abuse-deterrent labeling claims for the intranasal and intravenous routes.

2. Background

The misuse and abuse of prescription opioids is a serious and growing public health problem in the United States. With the increasing misuse and abuse of opioid analgesics, many companies are developing products which are intended to be abuse-deterrent by reformulating the opioid in a manner to make it difficult to abuse by one or more routes. RoxyBond was formulated using an abuse-deterrent technology that imparts physical and chemical barriers to make the product difficult to manipulate and abuse via the intranasal and intravenous routes. These abuse-deterrent properties may reduce abuse through manipulation; however, abuse by all routes is still possible. Importantly, abuse by the oral route, the most common route for an immediate-release opioid, is not addressed by this formulation. The abuse-deterrent technology used in RoxyBond is the same as that used in MorphaBond ER, an approved extended-release morphine product with abuse-deterrent features.

Oxycodone is listed under Schedule II of the Controlled Substance Act (CSA) and is currently approved and marketed in the United States in single-entity, immediate-release formulations; in combination with non-opioid analgesic drugs including acetaminophen, aspirin, and ibuprofen; and in single-entity extended-release formulations.

Oxaydo (oxycodone HCL) is the only IR opioid product with a description of data relevant to abuse-deterrence (i.e., a description of an intranasal human abuse potential study) in labeling; however, this labeling was approved prior to the issuance of the April 2015 abuse-deterrent guidance and is not consistent with that guidance. There are four approved extended-release oxycodone products, OxyContin (oxycodone HCl extended-release tablets), Targiniq (oxycodone HCl/naloxone HCl extended-release capsules), Xtampza ER (oxycodone HCl extended-release capsules), and Troxyca ER (oxycodone HCl/naltrexone HCl extended-release capsules), all of which have abuse-deterrent properties that are described in labeling consistent with the guidance.

The Division met with the Applicant at a Pre-IND meeting and provided several advice letters in response to the Applicant's questions throughout clinical development, where general agreement was reached on the regulatory approach, the required clinical development program, and the suitability of the PK data to bridge to the prior findings for the referenced product. Additionally, the Division provided advice regarding the in vitro and in vivo abuse-deterrence assessments. Agreement was reached that this product would not trigger the requirements under the Pediatric Research Equity Act (PREA).

3. Clinical/Statistical- Efficacy

No new clinical efficacy studies were submitted in support of this application. The exposure to oxycodone following dosing with RoxyBond is comparable to Roxicodone, based on relative bioavailability data, and the intended patient population is the same. Therefore, there

is an adequate scientific bridge to rely in the agency's previous finding of effectiveness for Roxicodone to support the efficacy of RoxyBond.

4. Safety

No new clinical safety studies were submitted in support of this application. The exposure to oxycodone following dosing with RoxyBond is comparable to Roxicodone, based on relative bioavailability data, and the intended patient population is the same. Therefore, there is an adequate scientific bridge to rely in the agency's previous finding of safety for Roxicodone to support the safety of RoxyBond.

The Applicant conducted four Phase 1 pharmacokinetic (PK) studies and one intranasal human abuse potential (HAP) study with the final-to-be-marketed formulation. The safety data from the PK studies were based on single-dose administration in healthy volunteers under naltrexone-blockade and are of limited value other than to demonstrate that there were not any issues with swallowing the formulation due to the (b) (4). The HAP study investigated the effects of intranasal administration of manipulated RoxyBond in opioid-experienced subjects.

The following five studies were reviewed for safety:

- Study O-ARIR-001(pilot comparative bioavailability study)
- Study O-ARIR-002 (human abuse potential study)
- Study O-ARIR-003 (clinical comparative bioavailability study)
- Study O-ARIR-004 (pilot dose proportionality study)
- Study O-ARIR-006 (dose proportionality study)

The Applicant's definitions of adverse events (AEs), serious adverse events (SAEs), and significant AEs were appropriate. With the exception of Study O-ARIR-001, AEs in the individual studies were collected and coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 17.1. Adverse events were summarized according to system organ class (SOC), preferred term (PT), and overall frequency. For Study O-ARIR-001, the AEs were listed per the verbatim term.

The safety population in the pharmacokinetic studies O-ARIR-001, O-ARIR-003, O-ARIR-004, and O-ARIR-006 was defined as all subjects dosed with the following study medications: naltrexone, Roxicodone, or RoxyBond. The safety population in the pharmacodynamic study (O-ARIR-002) includes all subjects randomized into the treatment phase.

The routine clinical testing conducted during the clinical trials appears adequate. Across all clinical studies, safety was assessed by monitoring for AEs, clinical laboratory measurements (chemistry, hematology, and urinalysis), vital signs, oxygen saturation, ECG, and physical examination. Safety was assessed at pre-specified time points with acceptable frequency. Nasal effects were assessed in Study O-ARIR-002 to address the potential safety risks associated with intranasal administration of drugs intended for oral use.

Exposure to Study Drug

A total of 366 subjects were exposed to the final to-be-marketed formulation of RoxyBond in the PK and HAP studies. The table below summarizes the cumulative exposure to RoxyBond and Roxicodone from clinical studies that used the final-to-be-marketed formulation.

Drug Product	**Dose, Route**	**O-ARIR-001** pilot	**O-ARIR-002** [a]	**O-ARIR-003**	**O-ARIR-004** pilot	**O-ARIR-006**	**Total**
RoxyBond	5 mg, oral	0	0	0	16	51	**67**
	15 mg, oral	0			16	54	**70**
	30 mg, oral	12 [b]	36	65 [c]	30	51	**194**
	30 mg, intranasal ground	0	35				**35**
Roxicodone	15 mg, intranasal crushed	0	208	0	0	0	**208**
	30 mg, oral	12	0	62	0	0	**74**
	30 mg, intranasal crushed	0	214 [d]	0	0	0	**214**

[a] Includes five subjects enrolled under original protocol and not included in final analysis
[b] All subjects received 2 doses of 30 mg RoxyBond, 1 fed dose and 1 fasted dose
[c] 60 subjects received 2 doses of 30 mg RoxyBond, 1 fed dose and 1 fasted dose
[d] 35 subjects received 2 doses of 30 mg Roxicodone intranasal crushed, 1 during the Drug Discrimination Test and 1 during the Treatment Period

(Source: Adapted from Applicant's table from the Integrated Summary of Safety, page 31)

Demographics

The demographics for each treatment group were similar, owing to the crossover design of these studies. All clinical studies were conducted in healthy subjects, with the exception of Study O-ARIR-002, which was conducted in healthy subjects who were experienced, nontherapeutic, recreational opioid users. The majority of subjects were male in all studies. The majority of subjects overall were white (140 subjects [73%]) followed by black/African American (34 subjects [18%]).

A summary of the demographic characteristics for the safety population by clinical study is presented in the table below:

Table 2.7.4-5. Summary of Demographic Characteristics by Individual Clinical Study (Safety Analysis Set)				
Clinical Study	N	Mean Age ± SD Median Age Range	Sex Female (%)/ Male (%)	Race N (%) American Indian/Alaska Native Asian Black/African American White Other/Multiracial/Not Reported
Bioavailability Studies				
O-ARIR-004	16	34.4 ± 9.4 31.0 23-53	13 (81.3)/ 3 (18.8)	0 0 2 (12.5) 13 (81.3) 1 (6.3)
O-ARIR-006	54	35.1 ± 10.4 34.0 19-55	10 (18.5)/ 44 (81.5)	0 1 (1.9) 29 (53.7) 15 (27.8) 9 (16.7)
Comparative Bioavailability/Bioequivalence Studies				
O-ARIR-001	12	29.0 ± 4.6 28.5 23-38	2 (16.7)/ 10 (83.3)	1 (8.3) 0 1 (8.3) 10 (83.3) 0
O-ARIR-003	75	25.7 ± 5.8 25.0 18-45	19 (25.3)/ 56 (74.7)	1 (1.3) 4 (5.3) 1 (1.3) 69 (92.0) 0
Healthy Subject Pharmacodynamic Study				
O-ARIR-002	36[a]	25.0 ± 5.72 24.0 19-41	5 (13.9)/ 31 (86.1)	0 1 (2.8) 1 (2.8) 33 (91.7) 1 (2.8)

N = number of subjects.
[a] = The report for *Study O-ARIR-002* omits 5 subjects who received treatment using a method that differed significantly from the other cohorts. This report reflects the actual information contained in the datasets.
Note: The safety population for the clinical studies.
Source: *Table 1* in Study O-ARIR-001, *Listing 16.2.4-2* in Study O-ARIR-002, *Table 11.2-1* in Study O-ARIR-003, *Table 3* in Study O-ARIR-004, and *Section 11.2* in Study O-ARIR-006.

(Source: Applicant's table from 2.7.4 Summary of Clinical Safety, page 14)

Major Safety Results

There were no deaths or nonfatal SAEs reported in any of the studies.

Overall, 12 subjects discontinued treatment due to AEs. Eight subjects were discontinued prior to randomization and treatment with RoxyBond or Roxicodone due to vomiting (6 subjects) or nausea (2 subjects) after naltrexone administration (all in Study O-ARIR-003). Three subjects discontinued due to an AE after receiving RoxyBond (headache, vomiting, and pruritus/lip swelling), and one subjects discontinued due to an AE after receiving Roxicodone (vomiting). Subject disposition by individual study for the safety population is presented below:

Table 2.7.4-4. Summary of Subject Disposition by Individual Clinical Study (Safety Analysis Set) (corrected)					
Reasons for Withdrawal	**O-ARIR-001 N = 12**	**O-ARIR-002 N = 36**	**O-ARIR-003 N = 75**	**O-ARIR-004 N = 16**	**O-ARIR-006 N = 54**
Total	3	2	17	1	3
Adverse event	0	0	10	0	2
Subject withdrawal	3	2	6	1	1
Lost to follow-up	0	0	1	0	0

N = number of subjects.
Source: *Section 13.2 in the Pharmacokinetic Report* for Study O-ARIR-001, *Listing 16.2.1-1* in Study O-ARIR-002, *Listing 16.2.1-1* in Study O-ARIR-003, *Listing 16.2.1* in Study O-ARIR-004, and *Listing 16.2.1* in Study O-ARIR-006.

(Source: Applicant's table from 2.7.4 Summary of Clinical Safety, page 13 submitted as a response to information request on January 9, 2017)

Discontinuations due to AEs are summarized by study below:

Adverse events leading to premature discontinuation (Study O-ARIR-003)

System Organ Class, No. (%)	**Naltrexone (N = 75)**	**Oxycodone (Fed) (N = 64)**	**Oxycodone (Fasted) (N = 61)**	**Roxicodone (N = 62)**
Overall	8 (10.7%)	1 (1.6%)	0 (0.0%)	1 (1.6%)
Gastrointestinal Disorders	8 (10.7%)	0 (0.0%)	0 (0.0%)	1 (1.6%)
Nausea	2 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Vomiting	6 (8.0%)	0 (0.0%)	0 (0.0%)	1 (1.6%)
Nervous System Disorders	0 (0.0%)	1 (1.6%)	0 (0.0%)	0 (0.0%)
Headache	0 (0.0%)	1 (1.6%)	0 (0.0%)	0 (0.0%)

(Source: Applicant's table from 12.3.1 Study Report, page 42)

- O-ARIR-006 (dose proportionality study) – Two subjects discontinued prematurely from Study O-ARIR-006 due to adverse events:
  - *Subject 45* experienced emesis 1 hour and 36 minutes after dosing with RoxyBond 15 mg in Period 1.
  - *Subject 47* experienced mild pruritus and mild lower lip swelling after the last PK sample collection in Period 1. The event resolved without treatment. The subject also had a small excoriated lesion on the chin, classified as not related to study drug.

Supportive Safety Results
Treatment-emergent adverse events (TEAEs) were reported in all studies. A summary of the incidence of TEAEs by clinical study is presented in the table below:

Incidence of TEAEs by clinical study

Clinical Study	Placebo n (%)	Naltrexone n (%)	Roxicodone n (%)	RoxyBond n (%)
O-ARIR-001 **N** **TEAE**	No placebo	12 4 (33%)	Not distinguished from RoxyBond[a]	12 4 (33%)
O-ARIR-002 **N** **TEAE**	34 1 (3%)	Not administered	35 16 (46%)	36 18 (50%)
O-ARIR-003 **N** **TEAE**	No placebo	75 21 (28%)	62 7 (11%)	65 18 (28%)
O-ARIR-004 **N** **TEAE**	No placebo	Not reported	Not administered	16 12 (75%)
O-ARIR-006 **N** **TEAE**	No placebo	Not reported	Not administered	54 27 (50%)

[a] Available data did not distinguish AEs by treatment, therefore, all AEs associated with oxycodone treatment were ascribed to RoxyBond

(Source: Adapted from Sponsor's table from 2.7.4 Summary of Clinical safety, page 16)

In all studies, the most common TEAEs by system organ class were gastrointestinal disorders, nervous system disorders, and skin and subcutaneous tissue disorders. The most common AEs were nausea, vomiting, headache, and pruritus.

Treatment-emergent AEs reported in ≥ 3% of subjects are summarized for each study below.

Study O-ARIR-001

A total of 16 TEAEs were experienced by five subjects during this study. Four subjects experienced AEs following treatment with naltrexone and four subjects experienced AEs following treatment with oxycodone. No subjects withdrew from this study.

TEAEs reported in ≥ 3% of subjects in study O-ARIR-001

Table 2.7.4-7.	**Summary of Treatment-emergent Adverse Events by System Organ Class and Preferred Term Reported in ≥ 3% of Subjects in Study O-ARIR-001**	
Adverse Event	**Naltrexone N = 12 n (%)**	**Oxycodone[a] N = 12 n (%)**
Number (%) of subjects with a TEAE	4 (33.3)	4 (33.3)
Feeling of warmth	1 (8.3)	0
Pea-sized swelling behind left ear	0	1 (8.3)
Nausea	2 (16.7)	1 (8.3)
Somnolence	0	1 (8.3)
Headache	1 (8.3)	1 (8.3)
Dizziness	1 (8.3)	1 (8.3)
Blurry vision	0	1 (8.3)
Rash on trunk	1 (8.3)	0

N = number of subjects enrolled per arm; n = number of subjects who had a TEAE (subjects are only counted once per arm); TEAE = treatment-emergent adverse event.
[a] = Available data did not distinguish AEs by treatment. Therefore, the data listed reflect data for all subjects exposed to ROXICODONE and Oxycodone ARIR.
Source: *Appendix E* in Study O-ARIR-001.

(Source: Sponsor's table from 2.7.4 Summary of Clinical safety, page 18)

Study O-ARIR-002 (HAL study)

A total of 62 TEAEs were reported by 27 subjects in this study; 37 events following administration of RoxyBond (oral or insufflated), 24 events following treatment with Roxicodone, and 1 event following the administration of placebo. The most common events were pruritus, nausea, and vomiting. The incidence of pruritus was similar between the Roxicodone and RoxyBond treatment groups. Vomiting occurred more frequently with RoxyBond. No subjects withdrew because of AEs.

TEAEs reported in ≥ 3% of subjects in study O-ARIR-002

Table 2.7.4-8. Summary of Treatment-emergent Adverse Events by System Organ Class and Preferred Term Reported in ≥ 3% of Subjects in Study O-ARIR-002

MedDRA System Organ Class Preferred Term	ROXICODONE N = 35 n (%)	Oxycodone ARIR Intranasal N = 35 n (%)	Oxycodone ARIR Oral N = 36 n (%)	Oxycodone ARIR Total N = 36 n (%)
Number (%) of subjects with a TEAE	16 (45.7)	10 (28.6)	14 (38.9)	18 (50.0)
Gastrointestinal disorders				
Nausea	4 (11.4)	4 (11.4)	3 (8.3)	5 (13.9)
Vomiting	2 (5.7)	3 (8.6)	3 (8.3)	5 (13.9)
Nervous system disorders				
Headache	2 (5.7)	0	1 (2.8)	1 (2.8)
Psychiatric disorders				
Irritability	2 (5.7)	0	0	0
Respiratory, thoracic, and mediastinal disorders				
Hiccups	2 (5.7)	0	0	0
Skin and subcutaneous tissue disorders				
Pruritus	0	0	4 (11.1)	4 (11.1)
Pruritus generalised	8 (22.9)	2 (5.7)	4 (11.1)	5 (13.9)
Vascular disorders				
Hot flush	2 (5.7)	0	1 (2.8)	1 (2.8)

MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects enrolled per arm; n = number of subjects who had a TEAE (subjects are only counted once per arm); TEAE = treatment-emergent adverse event.

(Source: Sponsor's table from 2.7.4 Summary of Clinical safety, page 19)

Study O-ARIR-003

A total of 85 TEAEs were reported by 32 subjects in the study; 42 events following the administration of naltrexone, 32 events following the administration of RoxyBond (19 events under fasted conditions and 13 events under fed conditions), and 11 events following the administration of Roxicodone. The most common adverse event was nausea (22 subjects; 15 following treatment with naltrexone, 11 following treatment with RoxyBond, and three following treatment with Roxicodone). Ten subjects withdrew from the study early because of AEs; eight after treatment with naltrexone (six for vomiting and two for nausea) and one each after treatment with RoxyBond (headache) and Roxicodone (vomiting).

TEAEs reported in ≥ 3% of subjects in study O-ARIR-003

Table 2.7.4-9. Summary of Treatment-emergent Adverse Events by System Organ Class and Preferred Term Reported in ≥ 3% of Subjects in Study O-ARIR-003

MedDRA System Organ Class Preferred Term	ROXICODONE N = 62 n (%)	Oxycodone ARIR Fed N = 64 n (%)	Oxycodone ARIR Fasted N = 61 n (%)	Oxycodone ARIR Total N = 65 n (%)
Number (%) of subjects with a TEAE	7 (11.3)	11 (17.2)	12 (19.7)	18 (27.7)
Gastrointestinal disorders				
Nausea	3 (4.8)	3 (4.7)	9 (14.8)	11 (16.9)
Vomiting	4 (6.5)	4 (6.3)	2 (3.3)	5 (7.7)
Nervous system disorders				
Dizziness	1 (1.6)	0	3 (4.9)	3 (4.6)
Headache	1 (1.6)	4 (6.3)	4 (6.6)	7 (10.8)

MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects enrolled per arm; n = number of subjects who had a TEAE (subjects are only counted once per arm); TEAE = treatment-emergent adverse event.
Source: *Listing 16.2.7-1* in Study O-ARIR-003.

(Source: Sponsor's table from 2.7.4 Summary of Clinical safety, page 20)

Study O-ARIR-004

A total of 30 TEAEs were reported by 12 subjects in this study. The frequency of TEAEs was similar for the different dose levels. The most common events were headache (4 subjects), somnolence (3 subjects), fatigue (2 subjects), and nausea (2 subjects). No subjects withdrew because of AEs.

TEAEs reported in ≥ 3% of subjects in study O-ARIR-004

Table 2.7.4-10. Summary of Treatment-emergent Adverse Events by System Organ Class and Preferred Term Reported in ≥ 3% of Subjects in Study O-ARIR-004

MedDRA System Organ Class Preferred Term	Oxycodone ARIR 30 mg N = 15 n (%)	Oxycodone ARIR 15 mg N = 16 n (%)	Oxycodone ARIR 5 mg N = 16 n (%)	Oxycodone ARIR 6 × 5 mg N = 15 n (%)	Oxycodone ARIR Total N = 16 n (%)
Number (%) of subjects with a TEAE	4 (26.7)	7 (43.8)	4 (25.0)	4 (26.7)	12 (75.0)
Gastrointestinal disorders					
Abdominal distension	0	0	0	1 (6.7)	1 (6.3)
Abdominal pain	1 (6.7)	0	1 (6.3)	0	2 (12.5)
Constipation	0	1 (6.3)	0	1 (6.7)	2 (12.5)
Dyspepsia	0	0	1 (6.3)	0	1 (6.3)
Nausea	0	2 (12.5)	1 (6.3)	0	2 (12.5)
Vomiting	0	0	1 (6.3)	0	1 (6.3)
General disorders and administration site conditions					
Fatigue	2 (13.3)	1 (6.3)	1 (6.3)	0	2 (12.5)
Feeling hot	0	1 (6.3)	0	0	1 (6.3)
Investigations					
Urinalysis abnormal NOS	0	0	1 (6.3)	0	1 (6.3)
Nervous system disorders					
Headache	1 (6.7)	2 (12.5)	0	1 (6.7)	4 (25.0)
Somnolence	1 (6.7)	1 (6.3)	0	2 (13.3)	3 (18.8)
Metabolism and nutrition disorders					
Decreased appetite	1 (6.7)	1 (6.3)	0	0	2 (12.5)
Musculoskeletal and connective tissue disorders					
Back pain	0	0	1 (6.3)	0	1 (6.3)
Respiratory, thoracic, and mediastinal disorders					
Nasal congestion	0	0	1 (6.3)	0	1 (6.3)
Skin and subcutaneous disorders					
Hyperhidrosis	0	1 (6.3)	0	0	1 (6.3)
Vascular disorders					
Pallor	0	1 (6.3)	0	0	1 (6.3)

MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects enrolled per arm; n = number of subjects who had a TEAE (subjects are only counted once per arm); NOS = not otherwise specified; TEAE = treatment-emergent adverse event.
Source: *Listing 16.2.7* in Study O-ARIR-004.

(Source: Sponsor's table from 2.7.4 Summary of Clinical safety, pp.21-22)

Study O-ARIR-006

A total of 59 TEAEs were reported by 27 subjects in this study. A lower proportion of subjects experienced AEs following administration of RoxyBond 5 mg compared to RoxyBond 15 and 30 mg. The most common events were nausea (7 subjects), headache (5 subjects), and somnolence (4 subjects). All of the events resolved spontaneously before study

completion. Two subjects withdrew because of AEs; one for lip swelling/pruritus and one for vomiting.

TEAEs reported in ≥ 3% of subjects in study O-ARIR-006

Table 2.7.4-11. Summary of Treatment-emergent Adverse Events by System Organ Class and Preferred Term Reported in ≥ 3% of Subjects in Study O-ARIR-006

MedDRA System Organ Class Preferred Term	Oxycodone ARIR 5 mg N = 51 n (%)	15 mg N = 54 n (%)	30 mg N = 51 n (%)	Overall N = 54 n (%)
Number (%) of subjects with a TEAE	7 (13.7)	19 (35.2)	14 (27.5)	27 (50.0)
Gastrointestinal disorders				
Constipation	0	2 (3.7)	0	2 (3.7)
Dry mouth	0	1 (1.9)	2 (3.9)	2 (3.7)
Flatulence	0	1 (1.9)	1 (2.0)	2 (3.7)
Nausea	0	6 (11.1)	1 (2.0)	7 (13.0)
Investigations				
ALT abnormal	0	0	2 (3.9)	2 (3.7)
Heart rate increased	1 (2.0)	0	1 (2.0)	2 (3.7)
Nervous system disorders				
Dizziness	1 (2.0)	2 (3.7)	1 (2.0)	3 (5.6)
Headache	0	3 (5.6)	3 (5.9)	5 (9.3)
Somnolence	0	3 (5.6)	2 (3.9)	4 (7.4)

ALT = alanine aminotransferase; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects enrolled per arm; n = number of subjects who had a TEAE (subjects are only counted once per arm); TEAE = treatment-emergent adverse event.
Source: *Section 12.2.2* in Study O-ARIR-006.

(Source: Sponsor's table from 2.7.4 Summary of Clinical safety, page 23)

The frequency of TEAEs was similar for the different dose levels of RoxyBond. The incidence of TEAEs in the PK study (O-ARIR-003) that included a Roxicodone arm was higher for RoxyBond compared to Roxicodone, in particular for the gastrointestinal events of nausea and vomiting and CNS events of headache and dizziness. The overall incidence of TEAEs was similar between the RoxyBond and Roxicodone arms in the HAP study, but vomiting occurred more frequently with RoxyBond compared to Roxicodone.

Conclusions
There were no unexpected adverse events associated with RoxyBond in the clinical studies conducted. The limited safety database is acceptable, as the safety of RoxyBond in the intended patient population is based on reliance on the agency's prior finding of safety for Roxicodone.

5. Advisory Committee Meeting

A joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) was held for this NDA on April 5, 2017. The committees were asked to discuss the overall risk-

benefit profile of the product and whether the Applicant has demonstrated abuse-deterrent properties for their product that would support labeling.

The following questions were asked of the committees:

1. **DISCUSSION**: Please discuss whether there are sufficient data to support a finding that RoxyBond (oxycodone hydrochloride immediate-release tablets) has properties that can be expected to deter abuse, commenting on support for abuse-deterrent effects for each of the following routes of abuse:
    a. Nasal
    b. Intravenous

2. **VOTE**: If approved, should RoxyBond be labeled as an abuse-deterrent product by the nasal route of abuse?

3. **VOTE**: If approved, should RoxyBond be labeled as an abuse-deterrent product by the intravenous route of abuse?

4. **VOTE**: Should RoxyBond be approved for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate?

Overall, the committees felt that the data presented at the meeting demonstrated that RoxyBond has properties that can be expected to deter abuse by both the intranasal and intravenous routes. However, several committee members expressed concerns over the potential toxicity associated with administration of the excipients, which were included in the formulation to confer the abuse-deterrent properties, by unintended routes (e.g., intravenous). Some of these committee members felt that additional testing should be performed on the extraction liquids to quantify the amounts of these excipients, whereas others felt labeling should be strengthened to warn about potential toxicities.

The committees overwhelmingly voted to label RoxyBond as an abuse-deterrent product by both the nasal (Question 2; 19 yes, 1 no) and intravenous (Question 3; 16 yes, 4 no) routes. The committee member who voted no for labeling the product as abuse-deterrent for the nasal route felt that abuse-deterrent formulations, in general, are not impactful in addressing the opioid epidemic and was concerned about the costs these products place on the healthcare system. Some of the members who voted no on the intravenous abuse-deterrent claim felt there were compelling data for this route; however, they expressed concern about the safety of the excipients when administered intravenously. Other members that voted no felt that the steps required to abuse this product by the intravenous route as a result of the formulation were not cumbersome enough to translate into an intravenous abuse-deterrent effect.

The committees voted to approve RoxyBond in the intended patient population (Question 4; 19 yes, 0 no, 1 abstain). However, the committees felt that the agency should require a safety evaluation of the excipients for the unintended intravenous route and that this could be done in a pre- or post-market setting.

6. Pediatrics

RoxyBond does not represent a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration, and, therefore, does not trigger the requirements under PREA.

7. Other Relevant Regulatory Issues

Abuse Deterrence

Xiaobin Shen, PhD, reviewed the in vitro abuse-deterrent studies with secondary concurrence by Julia Pinto, PhD. The Controlled Substance Staff (CSS) review was conducted by James Tolliver, PhD, with secondary concurrence by Martin Rusinowitz, MD, and Silvia Calderon PhD. The CSS statistical review was conducted by Anna Sun, PhD, with secondary concurrence by Qianyu Dang, PhD, and Yi Tsong, PhD.

The Applicant evaluated the in vitro abuse-deterrent characteristics of RoxyBond by conducting studies to assess physical manipulation using household tools, large volume extraction, and syringeability and small volume extraction. The highest strength of RoxyBond (30 mg) was used for the in vitro testing, with the 30 mg strength of Roxicodone as the comparator.

The Applicant conducted a study to evaluate the physical manipulation of RoxyBond using household tools, including a cheese grater, coffee grinder, hammer, knife, mortar and pestle, pill crusher, and spoon. The ability to reduce particle size using these tools was evaluated with and without pre-treatment with freezing at ≤0° C for 30 minutes, microwaving for 1 minute (800 W), or heating in a 150° C oven for 30 minutes. The agency requested evaluation of additional pretreatment conditions, including higher power microwaving for various durations.

Roxicodone was easily crushed into a fine powder suitable for insufflation using a glass pestle; Roxicodone did not provide any abuse-deterrent effects to physical manipulation. For RoxyBond, the coffee grinder was the only household tool tested that produced a powder suitable for insufflation. Increasing the grinding time (up to 10 minutes) did not substantially change the particle size distribution profile. The pretreatments did not meaningfully impact the results for any of the tools evaluated.

Large volume extraction studies were conducted using intact and crushed[2] samples in 30 ml of various solvents, including water, pH buffered solutions (pH 2, pH 4, pH 6, and pH 10), methanol, isopropyl alcohol, acetone, and ethanol (20%, 40%, and 100%). Solvents were evaluated at room temperature and 90°C,[3] with and without agitation at 100 rpm. Water and the pH buffered solutions were evaluated over 1, 5, 15, 30, and 60 minute time points. In contrast, the remaining solvents were evaluated at a fixed 30-minute time point. The effects of

[2] The large volume extraction studies utilized a coffee grinder for RoxyBond and a mortar and pestle for Roxicodone for the purposes of crushing the samples

[3] Volatile solvents were evaluated at room temperature only

microwaving and extraction of oxycodone from the tablet shell[4] after removal of the core were also evaluated. Roxicodone was easily extracted in water, which was further enhanced by crushing and increasing temperatures. Therefore, the Applicant did not evaluate additional solvents with Roxicodone.

The results of the large volume extraction studies demonstrated that oxycodone was most efficiently extracted from RoxyBond in low pH solvents and with high temperatures and agitation. The table below represents extraction of oxycodone from RoxyBond, expressed as mean percentage label claim (%LC), in low pH solvents. Crushing increased the extraction of oxycodone at the earlier time points; however, starting at 15 minutes and beyond, grinding slowed down extraction compared to intact tablets.

Solvent (with agitation 100 rpm)	RoxyBond Tablets 30 mg	Solvent Temperature	Mean %LC of Oxycodone Extracted (N = 3) Extraction Duration				
			1 Minute	5 Minutes	15 Minutes	30 Minutes	60 Minutes
pH 2 Solution (30 mL)	Intact	Room Temperature	0.0	1.0	2.5	25.4	66.2
	Ground		1.3	3.2	10.4	19.7	26.1
	Intact	90°C	0.5	9.6	85.8	93.8	93.4
	Ground		8.1	43.1	70.0	69.7	77.7
pH 4 Solution (30 mL)	Intact	Room Temperature	0.0	0.2	1.9	8.3	55.4
	Ground		1.4	2.7	17.9	21.2	31.9
	Intact	90°C	0.6	5.3	44.7	77.8	92.2
	Ground		20.6	26.1	42.2	56.6	56.8

Source: Dr. Tolliver's review, pg. 10

The table below represents extraction of oxycodone from RoxyBond, expressed as mean percentage label claim (%LC), with the remaining solvents.

Solvent (30 mL) (100 rpm)	Solvent Temperature	% LC of Oxycodone Extracted at 30 Minutes (N=3)	
		Intact RoxyBond 30 mg	Ground RoxyBond 30 mg
Tap Water	Room Temperature	1.2	4.7
	90°C	23.2	22.6
pH 6	Room Temperature	4.3	12.2
	90°C	34.4	38.8
pH 10	Room Temperature	1.0	13.0
	90°C	14.4	28.0
Methanol	Room Temperature	14.1	17.3
Ethyl Alcohol 20%	Room Temperature	1.3	8.3
Ethyl Alcohol 40%	Room Temperature	1.9	14.3
Ethyl Alcohol 100%	Room Temperature	1.0	4.3
Isopropyl Alcohol	Room Temperature	0.0	0.4
Acetone	Room Temperature	0.1	4.6

Source: Dr. Tolliver's review, pg. 11

Tap water, high pH solutions, and the remaining solvents were not efficient for extracting oxycodone from RoxyBond. Microwaving did not affect overall extraction. The overall

[4] The oxycodone is contained within the tablet shell.

extraction of oxycodone from the tablet shell in the pH 2 solution and water with microwaving was higher compared to tablets containing the core and without microwave treatment.

Small volume (5 and 10 ml water) extraction and syringeability studies were conducted on single and multiple intact, crushed (coffee grinder), and cut (kitchen knife) RoxyBond tablets, at 1, 5, 10, and 30-minute time points, at room temperature and 90°C, and with and without agitation. Syringeability was assessed using a 10 cc syringe fitted with 27, 24, and 18 gauge needles.

The Applicant demonstrated that Roxicodone can be used to easily generate solutions suitable for intravenous injection within one minute and using a 27 gauge needle.

Solutions generated from intact RoxyBond tablets were not suitable for intravenous injection. Although these solutions were syringeable through a 27-gauge needle indicating low viscosity, there was little extraction of oxycodone.

Extraction of crushed and cut RoxyBond tablets generated a viscous solution that required an 18-gauge needle to syringe. Dr. Tolliver noted the amount of oxycodone extracted in the 5 ml extraction could conceivably result in subjective reinforcing effects; however, it is unknown whether abusers would use the 18-gauge needle that was required to draw the solution into a syringe. The 10 ml extraction resulted in even lower concentrations of oxycodone due to the larger volume of fluid and the limited oxycodone recovery.

Two crushed RoxyBond tablets extracted in either 5 or 10 ml of water resulted in a viscous gel that could not be drawn into a syringe. Similarly, two cut RoxyBond tablets extracted in either 5 or 10 ml of water did not produce solutions suitable for injection; the 5 ml extraction resulted in no fluid and the 10 ml extraction resulted in limited amounts of fluid but with small quantities of oxycodone recovered.

The Applicant completed additional small volume extraction and syringeability studies in response to an agency information request during the review of the NDA, which included evaluating 10 ml of pH 2, pH 3.5, or pH 5 solvents using intact, ground, and core extracted tablets with and without microwave pretreatment. The results from these additional evaluations demonstrated recovery of non-viscous fluids, however, there was, in general, limited extraction of oxycodone. Two of the solutions, one pH 2 and one pH 3.5, resulted in oxycodone concentrations that Dr. Tolliver felt could result in some subjective reinforcing effects. However, it is unclear whether abusers could tolerate injection of these acidic solutions.

The Applicant additionally conducted an intranasal human abuse potential study (Study O-ARIR-002) to evaluate the abuse-deterrent effects of RoxyBond for the intranasal route. The study was a randomized, double-blind, double-dummy, active- and placebo-controlled, single-dose, four-way crossover study to determine the relative pharmacokinetics, pharmacodynamic (PD) effects, and safety of RoxyBond compared with Roxicodone when physically

manipulated[5] and administered intranasally to recreational, nondependent opioid users. Subjects were randomized and received the following treatments:

- Placebo Intranasal + Oral Placebo
- Crushed 30 mg Roxicodone Intranasal + Oral Placebo
- Ground 30 mg RoxyBond Intranasal + Oral Placebo
- Intact RoxyBond 30 mg Oral + Intranasal Placebo

The primary PD endpoint was Drug Liking, which was assessed using a bipolar visual analog scale (VAS) with the primary comparison between crushed Roxicodone and ground RoxyBond administered intranasally. Additional secondary PD endpoints included Drug High on a unipolar VAS, Take Drug Again on a bipolar VAS, and Overall Drug Liking on a bipolar VAS. PD measures included Emax (maximum (peak) effect) and TEmax (time to achieve Emax) among others.

Thirty-one subjects entered the treatment phase with 29 completers (2 subjects withdrew due to family emergencies).

The pharmacokinetic results are summarized in the table below:

Plasma Oxycodone Pharmacokinetic Parameter	Statistical Parameter	Active Treatments		
		RoxyBond 30 mg Intact, Oral	RoxyBond 30 mg Intranasal	Roxicodone 30 mg Intranasal
Cmax (ng/mL)	Mean (SD)	58.4 (13.1)	42.7 (13.5)	56.5 (11.5)
Tmax (hours)	Median (Range)	1.3 (0.6, 3.1)	2.3 (1.1, 4.1)	1.7 (0.6, 6.1)
AUC1hour (ng*hr/mL)	Mean (SD)	18.5 (11.2)	17.0 (7.9)	30.8 (7.6)

Source: Dr. Tolliver's review, pg. 22

Intranasal RoxyBond produced a significantly ($p<0.0001$) lower Emax of Drug Liking than intranasal Roxicodone. However, the Emax of Drug Liking for RoxyBond was higher than that of placebo. Results for Emax of Drug Liking are summarized below:

VAS	Treatment (IN – Intranasal)	Mean	Standard Deviation	Minimum	First Quartile	Median	Third Quartile	Maximum
Bipolar Drug Liking	Placebo IN	53.41	6.34	50.00	50.00	51.00	52.00	77.00
	Roxicodone 30 mg IN	82.86	11.55	50.00	79.00	82.00	91.00	100.00
	RoxyBond 30 mg IN	71.14	12.01	50.00	65.00	71.00	78.00	100.00
	Intact RoxyBond 30 mg Oral	81.48	11.49	56.00	75.00	82.00	89.00	100.00

Source: Dr. Tolliver's review, pg. 23

Intranasal RoxyBond produced a lower Emax of Take Drug Again compared to intranasal Roxicodone. Results for Emax of Take Drug Again are summarized below:

[5] RoxyBond – ground with a coffee grinder; Roxicodone – crushed with a mortar and pestle

VAS	Treatment	Mean Emax	Standard Deviation	Minimum	First Quartile	Median	Third Quartile	Maximum
Bipolar Take Drug Again	Placebo IN	41.86	20.09	0.00	49.00	50.00	50.00	78.00
	Roxicodone 30 mg IN	82.14	16.44	37.00	73.00	86.00	95.00	100.00
	RoxyBond 30 mg IN	62.24	24.51	3.00	50.00	62.00	81.00	99.00
	Intact RoxyBond 30 mg Oral	77.31	18.11	13.00	70.00	81.00	89.00	100.00

Source: Dr. Tolliver's review, pg. 26

Results for Emax of Drug High are summarized below:

VAS	Treatment (IN – Intranasal)	Mean	Standard Deviation	Minimum	First Quartile	Median	Third Quartile	Maximum
Unipolar High	Placebo IN	7.52	14.93	0.00	0.00	1.00	5.00	57.00
	Roxicodone 30 mg IN	66.34	25.69	0.00	56.00	74.00	84.00	96.00
	RoxyBond 30 mg IN	39.38	25.88	0.00	18.00	40.00	57.00	100.00
	Intact RoxyBond 30 mg Oral	66.66	25.92	1.00	49.00	72.00	85.00	100.00

Source: Dr. Tolliver's review, pg. 24

Results for Emax of Overall Drug Liking are summarized below:

VAS	Treatment (IN = Intranasal)	Mean Emax	Standard Deviation	Minimum	First Quartile	Median	Third Quartile	Maximum
Bipolar Overall Drug Liking	Ground Placebo IN	47.59	15.73	0.00	50.00	50.00	50.00	85.00
	Roxicodone 30 mg IN	80.86	14.60	35.00	73.00	85.00	90.00	100.00
	RoxyBond 30 mg IN	64.21	21.64	4.00	52.00	70.00	77.00	99.00
	Intact RoxyBond 30 mg Oral	78.55	17.41	13.00	73.00	83.00	89.00	100.00

Source: Dr. Tolliver's review, pg. 27

The pharmacokinetic and pharmacodynamic results described above support an abuse-deterrent effect of RoxyBond for the intranasal route. Dr. Tolliver noted that "RoxyBond tablets do not display a deterrent effect to oral abuse and may, following approval, be expected to be orally abused, as subjects in [the human abuse potential study] reported similar scores of subjective measures and shorter time to peak effects when taking intact RoxyBond to those reported when taking crushed Roxicodone intranasally."

The CMC and CSS reviewers concluded that the results of the in vitro studies suggest that RoxyBond is more difficult to prepare for intravenous and intranasal abuse as compared to Roxicodone. The CSS reviewers determined that the results of the in vitro and in vivo abuse-deterrent studies support potential abuse-deterrent effects of RoxyBond for the intravenous and intranasal routes. However, abuse by these routes may still occur.

We concur with the CSS and CMC reviewers' conclusions.

Clinical Site Inspection
The site where the intranasal human abuse potential study was conducted was not inspected as the investigator (Dr. Lynn Webster) and site have been inspected on two recent occasions for similarly conducted studies (July and September 2015) where no issues were identified.

Financial Disclosure
The Applicant provided financial information for the investigators who participated in the following clinical studies: ARIR-001, ARIR-002, ARIR-003, ARIR-004, and ARIR-006. There were no financial incentives considered to adversely affect the integrity of the data.

8. Labeling

The labeling for RoxyBond largely reflects the most recently updated labeling for Roxicodone. However, the basis for the abuse-deterrent properties of RoxyBond will be described in Section 9.2 of the labeling. Labeling is ongoing at the time of this writing.

9. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

  Approval

- Risk Benefit Assessment

  The clinical safety and effectiveness of RoxyBond are supported by relative bioavailability data bridging to the agency's prior findings for Roxicodone. Safety was additionally evaluated in the Phase 1 pharmacokinetic studies and the intranasal human abuse potential study. Although the safety database was limited for the reasons described in this review, no unexpected safety findings were observed for this immediate-release formulation of oxycodone. Importantly, no issues with swallowing the formulation due to the (b) (4) were identified.

  There are adequate data to support the Applicant's request to include the results of the assessment of the abuse-deterrent properties of RoxyBond and to conclude that RoxyBond is likely to deter abuse by the intranasal and intravenous routes of administration, although abuse by these routes, and the oral route of administration, is still possible. Postmarketing studies will be required to evaluate the impact of the formulation on real-world abuse.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

  None

- Recommendation for other Postmarketing Requirements and Commitments

1. In order to provide meaningful baseline data to support the hypothesis-testing studies which will be required under a separate PMR in the future, conduct a descriptive study that analyzes data on the following:

    1) Utilization of ROXYBOND and selected comparators. Reports should include nationally-projected quarterly dispensing data, overall and by age group and census region;

    AND

    2) Abuse of ROXYBOND and related clinical outcomes. These studies should utilize multiple data sources in different populations to establish the scope and patterns of abuse for ROXYBOND as well as mutually agreed-upon, selected comparators to provide context.

    - Data should include route-specific abuse outcomes, be nationally-representative or from multiple large geographic areas, and use meaningful measures of abuse.

    - Additional information, either qualitative or quantitative, from sources such as internet forums, spontaneous adverse event reporting, or small cohort studies may also be included to help better understand abuse of this drug, including routes and patterns of abuse in various populations.

    - Formal hypothesis testing is not necessary during this phase, but provide information on the precision of abuse-related outcome estimates (e.g., 95% confidence intervals for quarterly estimates) and calculate utilization-adjusted outcome estimates where possible.

2. Following satisfactory fulfillment of the listed above, you will be expected to conduct the following study:

    Conduct formal observational studies to assess whether the properties intended to deter misuse and abuse of ROXYBOND actually result in a meaningful decrease in misuse and abuse, and their consequences, addiction overdose, and death, in post-approval settings. The studies should allow FDA to assess the impact, if any, attributable to the abuse-deterrent properties of ROXYBOND and should incorporate recommendations contained in *Abuse-Deterrent Opioids—Evaluation and Labeling: Guidance for Industry* (April 2015).

Assessing the impact of the abuse-deterrent formulation on the incidence of clinical outcomes, including overdose and death, is critical to fulfilling this PMR. Any studies using electronic healthcare data should use validated outcomes and adhere to guidelines outlined in FDA's guidance for industry and FDA staff, *Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data*.

Because the formal observational studies are dependent on data collected in PMR 1, we are not attaching milestone dates for those studies *at this time*. At an appropriate time in the future, the language for these studies, the PMR set number, and the milestone dates will be formalized in a letter from FDA.

- Recommended Comments to Applicant

None

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

/s/

JOSHUA M LLOYD
04/14/2017
This review was completed in collaboration with Anjelina Pokrovnichka, MD.