Abuse-Deterrent Opioids – Evidence Evaluation & Labeling

Medication: Troxyca ER® (oxycodone extended-release/naltrexone)

Evaluation Date: 3/20/2017 Evaluation History: ☒ Initial Version 1.0, or ☐ Version _____

Current Product Labeling established: ☐ Prior to or ☒ After publication of FDA Guidance to Industry Document (4/2015)

This is a: (Check all that apply)

- ☒ New product
- ☐ Existing product, new formulation
- ☐ Existing product with new/updated labeling
- ☐ Other: _____

Product Abuse Deterrent Property Classification: – Check all that apply

- ☐ Physical / Chemical barrier
- ☒ Agonist / Antagonist combination
- ☐ Aversion
- ☐ Delivery System
- ☐ New Molecular entity or Prodrug
- ☐ Combination (check combined items)
- ☐ Novel Approach

Product Labeling:

Does the product have FDA abuse deterrent labeling? ☒ Yes or ☐ No Year obtained: 2016

Abuse Deterrent Evidence provided. Summary of in-depth literature review and product evaluation based on FDA Guidance to Industry Document

☒ Laboratory-based in vitro manipulation and extraction studies (Category 1)

Description of Research: *In vitro* data indicates crushing pellets results in the simultaneous release of oxycodone and naltrexone.

☒ Pharmacokinetic Studies (Category 2)

Description of Research: Pharmacokinetic studies indicate crushed Troxyca ER® resulted in similar oxycodone plasma exposures to equivalent doses of oxycodone IR. Crushed Troxyca ER® had similar oxycodone peak plasma concentration (C_{max}) to crushed oxycodone IR; however, C_{max} for crushed Troxyca ER® was approximately 4-fold higher than intact Troxyca ER® . Time to peak plasma concentration (T_{max}) was shorter for crushed Troxyca ER® (0.6 hour) compared to intact Troxyca ER® (12.1 hours).

☒ Clinical Abuse potential studies (Category 3)

Description of Research: Oral clinical abuse potential study assessed peak drug liking and peak drug high scores as co-primary endpoints after oral administration of intact and crushed Troxyca ER®, crushed oxycodone IR and placebo. Peak drug liking and drug high for both intact and crushed Troxyca ER® at all doses was significantly lower compared to equivalent doses of crushed oxycodone IR (P<0.0001).

☒ Clinical Abuse potential studies (Category 3)

Description of Research: Intranasal clinical abuse potential study assessed peak drug liking and peak drug high scores as co-primary endpoints after intranasal administration of crushed Troxyca ER®, crushed oxycodone IR and weight matched placebos. Peak drug liking and drug high scores were significantly lower for crushed Troxyca ER® compared to an equivalent dose of oxycodone IR (P<0.0001).

☒ Clinical Abuse potential studies (Category 3)

Description of Research: Simulated intravenous (IV) clinical abuse potential study assessed peak drug liking and peak drug high scores as co-primary endpoints after IV administration of simulated crushed

Troxyca ER®, IV oxycodone solution and IV placebo. Peak drug liking and drug high scores were significantly lower for simulated crushed Troxyca ER® IV solution compared to an equivalent dose of oxycodone IR IV solution (P<0.001).

☐ Additional Studies / Post Market data which assessed the impact of abuse-deterrent formulation (Category 4)

☐ Post market

☐ Formal studies included recommended study design features (see page 19 FDA Guidance document)
Description of Research: _____

☐ Determination if use of product results in meaningful reductions in abuse, misuse, and related adverse clinical outcomes, including addiction, overdose, and death
Description of Research: _____

☐ Outcome Measures and Data Interpretation in Abuse Potential Studies

- Standardized Instruments

☒ Visual Analogue Scales (VAS)
Description of Research: Drug liking, drug high, take drug again, any drug effects, bad drug effects, good drug effects, feel sick, nausea, sleepy and dizzy.

☐ Profile of Mood States
Description of Research: _____

- Data Interpretation

☒ Primary Analysis
Description of Research: Comparison of least squares means (LSM) of peak Drug Liking and Drug High VAS scores (E_{max} and AUE_{0-2}) (oral and IV studies); comparison of mean (95% CI) values of peak Drug Liking and Drug High VAS scores (E_{max} and AUE_{0-2}) (intranasal study);

☒ Statistical Analysis
Description of Research: Data analyzed using mixed-effect model with treatment, period, and sequence as fixed effects, and participant nested within sequence as random effect (all studies).

☒ Data and dropout for non-completers
Description of Research: Data regarding dropout and non-completers accounted for (all studies).

☐ None of the above

Strength of Evidence of Abuse Deterrent Properties:

☐ Evidence is based on physical/chemical property, theoretical assumptions or manufacturer's claims and is not yet supported by scientifically sound outcome data which demonstrates a reduction in the abuse of the product in the community setting compared to levels of abuse, overdose, and death that occurred when only formulations of the same opioid without abuse-deterrent properties were available (Category III)

☒ Evidence is based on physical/chemical property, clinical abuse potential studies or laboratory manipulation studies and is not yet supported by scientifically sound outcome data which demonstrates a reduction in the abuse of the product in the community setting compared to levels of abuse, overdose, and death that occurred when only formulations of the same opioid without-abuse-deterrent properties were available (Category II)

☐ There is evidence, supported by scientifically sound outcome data, which demonstrates a reduction in the abuse of the product in the community setting compared to levels of abuse, overdose, and death that occurred when only formulations of the same opioid without abuse-deterrent properties were available (Category I)