# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**204768Orig1s000**

# SUMMARY REVIEW

# Summary Review for Regulatory Action

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|---|---|
| **Date** | (electronic stamp) |
| **From** | Sharon Hertz, M.D. |
| **Subject** | Deputy Division Director Summary Review |
| **NDA #** | 204768/000 |
| **Applicant Name** | Iroko Pharmaceuticals |
| **Date of Submission** | April 30, 2013 |
| **PDUFA Goal Date** | February 28, 2014 |
| **Proprietary Name / Established (USAN) Name** | Tivorbex (indomethacin) |
| **Dosage Forms / Strength** | Capsules, 20 mg and 40 mg |
| **Proposed Indication(s)** | For the treatment of mild to moderate acute pain |
| **Action/Recommended Action:** | Approval |

| **Material Reviewed/Consulted** OND Action Package, including: | |
|---|---|
| Medical Officer Review | Anjelina Pokrovnichka, M.D., Ellen Fields, M.D., MPH |
| Statistical Review | Yan Zhou, Ph.D., Janice Derr, Ph.D. |
| Pharmacology Toxicology Review | Alex Xu, Ph.D., Adam Wasserman, Ph.D. |
| CMC Review | Xiaobin Shen, Ph.D., Prasad Peri, Ph.D. |
| OBP Review | Elsbeth Chikhale, Ph.D., Agelica Dorantes, Ph.D. |
| Clinical Pharmacology Review | Suresh Naraharisetti, Ph.D., Yun Xu, Ph.D. |
| OSI | Cynthia F. Kleppinger, M.D., Janice Pohlman, M.D., M.P.H. |
| CDTL Review | Ellen Fields, M.D. , MPH |
| OSE/DMEPA | Vicky Borders-Hemphill, Pharm.D., Irene Z. Chan, Pharm.D., BCPS |
| OPDP/DCDP | L. Shenee Toombs, Pharm.D. |
| OMP/DMPP | LaShawn Griffiths, MSHS-PH, BSN, RN, Barbara Fuller, RN, MSN, CWOCN |
| CMC Microbiology | Erika Pfeiler, Ph.D. |
| Pediatric and Maternal Health Staff | Donna Snyder, M.D., Hari Cheryl Sachs, M.D. Miriam Dinatale, M.D., Jeanine Best, M.D. |

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication ErrorsPrevention
DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OPDP=Office of Prescription Drug Promotion
DCDP=Division of Consumer Drug Promotion
OMP=Office of Medical Policy Initiatives
DMPP=Division of Medical Policy Programs



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# Signatory Authority Review Template

## 1. Introduction

This is a 505(b)(2) new drug application for Tivorbex, a new immediate-release capsule formulation of indomethacin. The referenced product is NDA 016059, Indocin, an immediate-release formulation of indomethacin initially approved in 1965. Indocin has been discontinued, not due to either safety or efficacy reasons, therefore, the Applicant was able to conduct relative bioavailability studies with ANDA 070624 (Mylan Pharmaceuticals, Inc.) to create the scientific bridge for relying on the Agency's prior findings of safety and efficacy for indomethacin. The key issues that will be discussed in this review are the Applicant's theory about the effect of a smaller particle size of indomethacin in this formulation.

## 2. Background

The Applicant conducted the clinical development program under IND 101,940 and proposes to market Tivorbex in two capsule strengths, 20 mg and 40 mg to be dosed three times daily, and 40 mg twice daily. The application is supported by a relative bioavailability and food effect study, a Phase 2 single-dose study and two Phase 3 efficacy studies, along with relying on the Agency's prior finding of efficacy and safety of Indocin. The Applicant developed Tivorbex as a new formulation of indomethacin with reduced particle size, intended to promote the dissolution and absorption of indomethacin. However, the absorption of indomethacin from Indocin is nearly 100% following oral administration. The Applicant claimed that the improved dissolution properties of Tivorbex would be associated with rapid absorption resulting in comparable pain relief to Indocin at an approximately 20% lower dose, although they did not conduct any studies with Indocin as an active comparator. For further details about the development program, refer to reviews by Drs. Fields and Pokrovnichka.

## 3. CMC/Device

DMF (b) (4) held (b) (4) supports the drug substance and was found to be acceptable. As noted by Dr. Shen:

> The 20 mg and 40 mg drug product capsules are (b) (4) encapsulated in hard gelatin capsule shells. There are no novel excipients and none are used at levels that exceed prior approved oral products.

The commercial manufacturing process involves (b) (4) a small particle size referred to as submicron by the Applicant, similar to



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what was done for the Applicant's product, Zorvolex, an immediate-release diclofenac. As noted in the clinical pharmacology review, the Applicant's claim (b) (4) will improve the bioavailability of the drug product has not been demonstrated.

The proposed dissolution method and dissolution acceptance criteria were found to be acceptable. The Applicant's request for elimination of specified microorganism testing for product release was found to be acceptable.

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance, and with the categorization of the particle size as submicron. Manufacturing site inspections were acceptable. The Applicant's request for a categorical exclusion (21CFR25.31(a)) is supported by the their argument that approval of Tivorbex will "not increase overall use" of indomethacin as Tivorbex will compete with existing approved applications. Stability testing supports an expiry of 24 months. There are no outstanding issues.

## 4. Nonclinical Pharmacology/Toxicology

Five known impurities were identified in the drug substance and drug product, all below the qualification threshold levels described by ICH Q3A and ICH Q3B. The CMC review identified structural alerts for genotoxicity for three of the drug product-related impurities, but the Applicant conducted a computational toxicity evaluation of all five. The Applicant's evaluation predicted that all five would be negative in the Ames assay and others. The CDER computational toxicity group, however, predicted that two of the drug product impurities, (b) (4) would be positive for genotoxicity in the Ames assay.

As noted by Dr. Xu (p 5):

> When QSAR prediction results are positive, further actions are usually needed. These include decreasing the level of the impurities to an acceptable daily intake level with minimal carcinogenicity concern, or conducting further studies such as the actual Ames assay to confirm the prediction results. Tivorbex is indicated for acute pain and the maximum recommended dose is 120 mg; therefore, the maximal total daily intake for these impurities is (b) (4) This is above the acceptable intake level of total genotoxic impurities for a drug product indicated for acute use. Based on the Agency's current thinking, the daily intake of genotoxic impurities may not exceed 120 μg/day for a drug product with < 1 month treatment period. However, the impurity specification limit of the indomethacin drug substance used in Tivorbex are consistent to those indomethacin drug substances manufactured according to DMF (b) (4) file which have been used for other FDA- approved drug products. Based on the Agency's current policy, impurities formed in the drug substance are not to be assessed retrospectively if it is used in an approved product and there is no change in the drug substance synthesis. Therefore, this issue was not further pursued.

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



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## 5. Clinical Pharmacology/Biopharmaceutics

The referenced product for this 505(b)(2) application is NDA 016059, Indocin, an immediate-release formulation of indomethacin initially approved in 1965. Indocin has been discontinued, not due to either safety or efficacy reasons, therefore, the Applicant was able to conduct relative bioavailability studies with ANDA 070624 (Mylan Pharmaceuticals, Inc.) to create the scientific bridge for relying on the Agency's prior findings of safety and efficacy for indomethacin. As noted by Dr. Naraharisetti, the bioavailability of indomethacin following oral administration of Indocin was nearly 100%, with 90% absorbed within 4 hours.

(b) (4)

The one clinical pharmacology study conducted with the final formulation, IND1-12-07, was a relative bioavailability, dose proportionality, and food effect study. Compared to indomethacin 50 mg capsules, the 40 mg Tivorbex resulted in a 20% lower AUC with a comparable Cmax. The Tmax was 21 minutes earlier. The half-life of indomethacin was the same for both formulations. The food effect was comparable for both formulations, and for Tivorbex, delayed Tmax by 1.3 hours and decreased Cmax by 46% and AUC by 9%. Because the gastrointestinal symptoms associated with NSAIDs may be reduced when taken with food, it is usual for patients to take these drugs with food. The dose normalized PK parameters show that the 20 and 40 mg capsules result in dose proportional Cmax and AUC under fasted conditions.

The proposed dissolution method and dissolution acceptance criteria were found to be acceptable.

The Applicant developed Tivorbex to have a greater extent of absorption than Indocin and has failed to demonstrate this to be the case. The relative bioavailability study demonstrated comparable extent of exposure when adjusted for dose, so that Tivorbex represents a smaller dose of indomethacin than is available with Indocin-based generic products. I concur with the conclusions reached by the clinical pharmacology reviewer and biopharmaceutics reviewer that there are no outstanding clinical pharmacology or biopharmaceutics issues that preclude approval.

## 6. Clinical Microbiology

N/A

## 7. Clinical/Statistical-Efficacy

The efficacy of Tivorbex was evaluated in two randomized, double-blind, placebo-controlled studies in patients undergoing surgical repair of bunionectomy, Study IND3-08-04b and Study IND3-10-06 (in this review, referred to as Studies 04b and 06, respectively). Subjects were



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adults with pain between 40 and 100 mm on a visual analog scale once the anesthetic block wore off. Subjects were randomized to Tivorbex 20 mg three times a day, Tivorbex 40 mg twice daily, Tivorbex 40 mg three times daily, and placebo in both studies and in one study, to an additional treatment group, celecoxib 200 mg twice daily after a 400 mg first dose. Hydrocodone 10 mg/acetaminophen 325 mg was available as rescue as needed. The primary efficacy analysis was the summed pain intensity difference over 48 hours (SPID 48), with a sequential testing procedure to control for multiplicity due to the three Tivorbex arms. The celecoxib analysis was not part of the primary analysis. Further details of the study design can be found in Dr. Pokrovnichka's review.

Both studies randomized 91 to 94 patients per treatment group and had completion rates from 97 to 100%. The low dropout rate limits the impact of imputed data due to dropouts. However, 89% of subjects in Study 04b and 80% of subjects in Study 06 used rescue medication. Traditionally, a pain score is measured prior to the use of rescue and that score is used for any scores that would have been influenced by rescue. The sponsor failed to use this method in these efficacy trials, and instead, imputed the baseline score for all pain scores subsequent to the use of rescue. For a symptomatic treatment with a limited duration of effect, this extreme degree of imputation is not appropriate. To understand the effect of the high use of rescue, and to evaluate the effect of the Applicant's approach to handling pain scores after rescue use, Dr. Zhou conducted additional sensitivity analyses in which the pre-rescue pain scores were carried forward to the next pain assessment if available. In all of the Applicant's and Dr. Zhou's analyses, efficacy was demonstrated for the 40 mg twice daily and 40 mg three times daily doses, compared to placebo. While the Applicant's primary analysis of the Tivorbex 20 mg three times daily dose in Study 06 failed to meet statistical significance, this appears to have been an artifact of the method of imputation used. The Applicant's sensitivity analyses and the analyses conducted by Dr. Zhou more appropriately reflect the actual experience of the patient and confirm the efficacy of the 20 mg three times daily dose. Dr. Zhou concluded that both studies support a finding of efficacy for Tivorbex 20 mg three times daily, 40 mg twice daily, and 40 mg three times daily when compared to placebo in the study population. Time to onset of effect was measured inpatients reporting onset within four hours after recovery from regional anesthesia using two stopwatches during the inpatient period following surgery. The median time to onset was under one hour for patients randomized to Tivorbex and was based on 60% of the Tivorbex group who reported onset within the four-hour window.

The data also support a finding of efficacy for celecoxib as compared to placebo in Study 04b. However, as celecoxib was included in only one of the two studies, no comparative statements can be made in labeling or in promotional materials concerning Tivorbex and celecoxib. In addition, there is no need to include information pertaining to celecoxib in the labeling.

In comparison to the referenced product, Indocin, with 25 mg and 50 mg strengths for twice daily or three times daily, only the 40 mg Tivorbex has efficacy demonstrated to support twice and three times daily dosing, the 20 mg dose has data supporting only three times daily dosing.



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## 8. Safety

The assessment of safety is based primarily on data from the Phase 3 efficacy studies. A total of 735 subjects received at least one dose of Tivorbex capsules, including 80 healthy subjects in Phase 1 trials, 101 subjects in the Phase 2 trial, and 554 subjects in the Phase 3 trials. There were no new safety concerns identified for exposures up to 48 hours as compared to the labeling for Indocin. There were no deaths in patients treated with Tivorbex. One reported serious adverse event in a patient randomized to Tivorbex was a case of DVT. Although not listed as serious, there was one case of angioedema and two cases of urticaria in patients randomized to Tivorbex.

It is difficult to assess the adverse events specific to Tivorbex in this population as more than 80% of subjects received rescue doses of an opioid during the study. Therefore, the reporting of adverse reactions in the package insert includes some events that were more frequent in placebo patients who relied on opioids for analgesia in the postoperative periods in order to provide some information about the frequency of adverse events with Tivorbex. The most frequent treatment emergent adverse events occurring in at least 5% of patients in a Tivorbex or placebo treatment group were edema, nausea, headache, dizziness vomiting, hematoma, and constipation.

Tivorbex will have the class language in the package insert including all of the same warnings as Indocin and will have the NSAID class medication guide.

## 9. Advisory Committee Meeting

No advisory committee was convened for this application.

## 10. Pediatrics

In the past, DAAAP had granted waivers for pediatric patients below the age of 1 for diclofenac products due to immaturity of the CYP 2C9 enzyme system, the major metabolic pathway for diclofenac, and also for indomethacin. The Applicant has requested a waiver of studies (b) (4) However, the Pediatric Research Committee has advised that when products represent a meaningful therapeutic benefit over existing therapies for pediatric patients, studies should be conducted, even when metabolic systems are immature. There are approved indomethacin products in formulations suitable for use in children. Based on a review of IMS Health Systems by the Applicant, a total of 14,034 patients ages 0 to 17 years of age were prescribed indomethacin with less than 500 of these younger than 6 years of age. The most frequent uses of oral indomethacin in pediatric patients were for treatment of gout, followed by headache and connective tissue disorders. Dr. Snyder notes that indomethacin is approved for use in neonates to close a patent ductus arteriosus (PDA) but is not approved for treatment of acute pain and that it is used off-label in patients with Juvenile Idiopathic Arthritis



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(JIA)[1] and to treat certain uncommon headache disorders such as paroxysmal hemicrania and hemicrania continua.[2] In contrast, the American Academy of Pediatrics (AAP) Committee on Pediatric Emergency Medicine and Section on Anesthesiology and Pain Medicine does not include indomethacin as a recommended treatment for acute pain in pediatric patients in an emergency room setting.[3] Additionally, an extensive literature review did not support use in pediatrics for the acute pain indication.

Also noted by Dr. Snyder:

> The sponsor sites a statement included in labeling on hepatotoxicity noted in JIA patients and a statement that indomethacin "should not be prescribed for pediatric patients 14 years of age and younger unless toxicity or lack of efficacy associated with other drugs warrants the risk" to support their argument. However, the labeling also states that "in experience with more than 900 pediatric patients reported in the literature or to the manufacturer who were treated with Capsules INDOCIN, side effects in pediatric patients were comparable to those reported in adults." The information supplied by the sponsor does not support an age dependent safety risk. This rationale alone would not be sufficient to issue a waiver on the grounds that the product would be unsafe to use in this population if use is anticipated.

Therefore, the following studies are required under PREA, and the timeline was agreed upon with the Applicant and approved by the Pediatric Research Committee (PeRC) on January 15, 2014. PeRC recommended that the Division request a more accelerated timeline for the studies than originally proposed by the Applicant, however in order to maintain consistency with a recently approved product from the same Applicant, the timeline was not changed.

- Study 1: An open-label pharmacokinetic and safety study or studies of an age appropriate formulation of indomethacin in pediatric patients 6 through less than 17 years of age
- Study 2: An open-label pharmacokinetic and safety study or studies of an age appropriate formulation of indomethacin in pediatric patients 2 through 6 years of age
- Study 3: A pharmacokinetic, safety, and efficacy study or studies of an age appropriate formulation of indomethacin in pediatric patients 1 through 2 years of age

[1] Hugel, B. et al. Treatment Preferences in juvenile idiopathic arthritis - a comparative analysis in two health care systems. Pediatric Rheumatology: 2013. 11:3

[2] Summ, O. and Evers, S. Mechanism of Action of Indomethacin in Indomethacin-Responsive Headaches. Curr Pain Headache Rep (2013) 17:327

[3] Fein, J.A., et al., Relief of pain and anxiety in pediatric patients in emergency medical systems. Pediatrics, 2012. 130(5): p. e1391-405.



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The timetable for completion of the studies is as follows, noting that the age range for the older children is through less than 17, not 18 years:

| Clinical Trials | Final Protocol Submission Date | Trial Start Date | Trial Completion Date | Final Report Submission |
|---|---|---|---|---|
| 6 years to < 18 years (Trial 1) | April 1, 2015 | October 1, 2015 | February 1, 2017 | October 2, 2017 |
| 2 years to < 6 years (Trial 2) | November 2, 2015 | June 1, 2016 | October 2, 2017 | June 1, 2018 |
| 1 year to < 2 years (Trial 3) | June 1, 2018 | December 31, 2018 | April 30, 2021 | December 31, 2021 |

## 11. Other Relevant Regulatory Issues

The Office of Scientific Investigations (OSI) inspected three clinical study sites that participated in one or both of the Phase 3 studies, and the CRO (Premier Research). The classification for each is "No Action Indicated." According to the OSI review, the study data appear reliable in support of this NDA. The review states that the observations noted for the inspections are based on the preliminary review of the Establishment Inspection Reports. OSI will generate an inspection summary addendum if conclusions change upon OSI final classification. OSI classification of inspection is finalized when written correspondence is issued to the inspected entity. If the classification does not differ from the preliminary classification included in the clinical inspection summary, no statement with a final recommendation is issued.

Also as noted by Dr. Fields:

- The Applicant submitted Form FDA 3454 "Certification: Financial Interests and Arrangements of Clinical Investigator", with a list of all investigators for the Phase 1, Phase 2, and Phase 3 clinical trials, certifying that they had no financial interests or arrangements to disclose.
- The application was discussed on January 21, 2014 at the 505(b)(2) clearance meeting, and was cleared for action from a 505(b)(2) perspective

There are no other unresolved relevant regulatory issues.

## 12. Labeling

The proprietary name of Tivorbex was found acceptable. Reviews of the package insert, medication guide, and carton and container labels were conducted, as appropriate by OSE's Division of Medication Error Prevention and Analysis, OMP's Division of Medical Policy Programs, and OPDP's Division of Consumer Drug Promotion and comments were conveyed to the Applicant for inclusion in labeling. However, changes that would make the labeling



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different than the class language used for NSAIDs were deferred until further class-related labeling changes are implemented in the future.

The Maternal Health Team provided labeling recommendations for the Pregnancy section of the label that were incorporated into the package insert.

The Applicant sought (b) (4) which was found to be unacceptable by the CMC team. (b) (4)

## 13. Decision/Action/Risk Benefit Assessment

- Regulatory Action - Approval

- Risk Benefit Assessment

Tivorbex is a novel formulation of indomethacin intended for the management of mild to moderate pain. There is evidence of efficacy from two adequate and well-controlled trials. There is evidence of safety from the same clinical trials as well as through reliance on the Agency's prior findings of efficacy and safety for Indocin. Indocin is indicated for a number of conditions other than acute pain. Regarding the formulations, the primary differences between Tivorbex and Indocin are the strengths and dosing frequency offered, with Tivorbex available as 20 mg capsules for three times daily dosing and 40 mg capsules for twice daily and three times daily dosing compared to Indocin 25 and 50 mg strengths for twice or three times daily dosing.

Based on the data provided, Tivorbex represents a lower strength formulation of indomethacin, but there is no evidence for enhanced absorption based on the particle size. In the absence of comparative studies, it is unknown, what if any difference may be present in the adverse event profile of Tivorbex. Therefore, the full NSAID class labeling will apply and no comparative safety claims may be made with Indocin. In addition, as celecoxib was included in only one of two efficacy studies, no comparative claims may be made with celecoxib.

- Recommendation for Postmarketing Risk Management Activities

None



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- Recommendation for other Postmarketing Study Commitments

The only post marketing requirements are those required under the Pediatric Research Equity Act:

**Study 1**: An open-label pharmacokinetic and safety study or studies of an age-appropriate formulation of indomethacin in pediatric patients 6 to < 17 years of age with acute pain

**Study 2**: An open-label pharmacokinetic and safety study or studies of an age-appropriate formulation of indomethacin in pediatric patients 2 to < 6 years of age with acute pain

**Study 3**: A pharmacokinetic, safety, and efficacy study or studies of an age-appropriate formulation of indomethacin in pediatric patients 1 to < 2 years of age with acute pain



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/s/

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SHARON H HERTZ
02/24/2014