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APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	February 3, 2014
From	Ellen Fields, MD, MPH Clinical Team Leader, DAAAP
Subject	Cross-Discipline Team Leader Review
NDA #	204768
Applicant	Iroko Pharmaceuticals, LLC
Date of Submission	April 30, 2013
PDUFA Goal Date	February 28, 2014
Proprietary Name / Established (USAN) names	Tivorbex(indomethacin) Capsules
Dosage forms / Strength	Oral capsules, 20 mg and 40 mg
Proposed Indication(s)	Treatment of mild-to-moderate acute pain
Recommended:	Approval

1. Introduction

Iroko Pharmaceuticals, LLC (the Applicant) submitted this New Drug Applicant (NDA) for Tivorbex capsules, an immediate-release formulation of indomethacin, for the treatment of mild-to-moderate acute pain in adults. The Applicant conducted the clinical development program under IND 101,940, and plans to market Tivorbex in two capsule strengths, 20 mg and 40 mg, to be taken by mouth two or three times per day (20 mg TID, 40 mg BID or TID)

Indomethacin is a nonsteroidal anti-inflammatory drug (NSAID) with antipyretic, anti-inflammatory, and analgesic properties, which are due to decreased prostaglandins in peripheral tissues mediated by inhibition of cyclooxygenase (COX) enzymes involved in the synthesis of prostaglandins. Specifically, indomethacin is a non-specific inhibitor of COX 1 and 2 enzymes. Indomethacin was first approved in the US in 1965 as Indocin 25 mg and 50 mg capsules, indicated for the management of moderate to severe pain in conditions such as rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, acute painful shoulder, and acute gouty attack. Indocin has since been discontinued from the market for reasons not due to safety or efficacy, and there are several generic products available (oral capsules, oral suspension, suppository, injectable). Indomethacin is also approved as an injectable formulation to close a hemodynamically significant patent ductus arteriosus in premature infants.

The Applicant submitted this NDA under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act referencing the approved product, Indocin, NDA 16059. Because Indocin is no longer available, the Phase 1 biolinking trials were conducted using Indomethacin 50 mg capsules (ANDA 70624, Mylan Pharm.)

The NDA submission consists of chemistry, manufacturing, and controls (CMC) information, nonclinical information, biopharmaceutics data, and clinical pharmacology and clinical data from six trials, two Phase 1 pharmacokinetic (PK) studies (IND1-08-01 and IND1-12-07), one

Phase 2 proof-of-concept study (IND3-08-04b), and two Phase 3 clinical trials (IND3-08-03 and IND3-10-06) in patients undergoing bunionectomy. The to-be-marketed formulation was used in the Phase 1 study (IND1-12-07) and in both Phase 3 trials. A proof-of-concept formulation was used in the other Phase 1 trial and the Phase 2 trial.

This NDA submission was given a standard review designation. This review will cover the key findings of all review disciplines and any important issues that arose during the review cycle.

2. Background

The Applicant developed Tivorbex as an immediate-release formulation of indomethacin to "address the need for lower-dose indomethacin options for the treatment of mild to moderate acute pain." Tivorbex capsules contain 20% less of the active ingredient compared to the previously approved oral indomethacin products. The Applicant maintains that the manufacturing technology used to reduce the indomethacin drug substance particle size in Tivorbex will enhance the rates of dissolution (b) (4) However, the previously approved indomethacin capsules are 100% bioavailable following oral administration and time to peak concentration is approximately two hours. Additionally, the Applicant did not provide any comparative data between Tivorbex and indomethacin capsules in order to make comparative safety or efficacy claims or to substantiate their rationale.

During development, the Applicant designated their formulation as a "nanoformulation", (b) (4) The Division informed the Applicant, during the End-of-Phase 2 meeting (June, 2010), that their formulation does not meet the Agency's definition of a nanoformulation as the particle size must be ≤100 nm to qualify for that designation. The Applicant subsequently referred to their formulation as a "submicron" formulation.

The Division held End-of-Phase 2 and Pre-NDA meetings with the Applicant during clinical development where agreement was reached on the overall clinical development program. The Applicant conducted two adequate and well-controlled clinical efficacy trials in post-operative bunionectomy patients with acute pain. A safety database of at least 500 patients was required barring any unexpected safety signals.

3. CMC/Device

The CMC review was conducted by Xiaobin Shen, Ph.D., with secondary concurrence by Prasad Peri, Ph.D. The key findings from Dr. Shen's review are summarized below. The CMC team recommended approval.

The indomethacin drug substance is referenced to DMF (b) (4) which was deemed adequate. It is manufactured (b) (4) This site has satisfactory EES status. The drug substance is packaged (b) (4) The drug substance stability data was referenced to DMF (b) (4) which supports a retest period (b) (4)

The drug product is available as 20 mg and 40 mg capsule strengths. Both strengths have the same composition. (b) (4) The excipients are of USP/NF grade. The capsules are packaged in HDPE bottles as 30 and 90 count commercial products (b) (4) The drug product is manufactured (b) (4) and packaged (b) (4) Both sites have satisfactory EES status.

Drug substance and product specifications provide adequate controls. The stability data for the drug product provided by the Applicant support the proposed 24-month expiry. The CMC team did not recommend any postmarketing commitments.

4. Nonclinical Pharmacology/Toxicology

The nonclinical review was conducted by Zengjun Xu, Ph.D., with secondary concurrence by Adam Wasserman, Ph.D. The key findings from Dr. Xu's review are summarized below. The nonclinical team recommended approval.

No new nonclinical studies were included in this NDA submission. The maximum labeled dose for Tivorbex is 40 mg TID, which is less than the maximum dose of Indocin, 50 mg TID, so the nonclinical data for the reference drug covers the clinical exposure resulting from Tivorbex. Additionally, the treatment duration of Tivorbex does not exceed that of Indocin. Therefore, nonclinical toxicity studies were not necessary for this NDA. The excipients in the drug formulation are not novel (b) (4) All impurities in the drug substance are below the qualification level as required by the ICH Q3A and Q3B guidance. The Applicant also provided justification of the residual solvent levels in the drug substance according to ICHQ3C.

The Applicant conducted a computational toxicity analysis, which is also known as quantitative structure relationship analysis (QSAR), to investigate the potential for genotoxicity. The following discussion is taken from Dr. Xu's review:

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.

Based on the current thinking of the Agency, only the computational toxicology prediction for the Ames assay is considered appropriate for regulatory support because the datasets used for prediction of other endpoints are not robust and sufficiently validated for use. If the computational analysis for Ames assay is negative, there is no need to further investigate the genotoxicity potential of an impurity. In addition, the Agency requires that the computational toxicity analysis should be conducted in at least 2 prediction systems with one using statistical correlations and the other expert rule-based. In the analysis conducted by the Applicant, only MC4PC system (a prediction model using statistical correlations) was used. The structures of these compounds were sent to CDER computational toxicity group (CTG) for analysis of the association of the structures with the potential activity in Ames assay using MC4PC system and another knowledge-based system, Leadscope Model Appliers (LMA). Both MC4PC and LMA systems use statistical correlations to make predictions. In addition, the Derek system which uses expert rules for prediction was also used in the analysis conducted by CTG. The results of the analysis predicted that (b) (4) would be positive in Ames assay.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology review was conducted by Suresh Naraharisetti, Ph.D., with secondary concurrence by Yun Xu, Ph.D. The Biopharmaceutics review was conducted by Elsbeth Chikhale, Ph.D., with secondary concurrence by Anjelica Dorantes, Ph.D. and Richard Lostritto, Ph.D. The key findings from their reviews are summarized below. Both teams have recommended approval.

Clinical Pharmacology

Mechanism of Action

TIVORBEX is a nonsteroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic and analgesic properties.

The mechanism of action of TIVORBEX like that of other NSAIDs, is not completely understood but involves inhibition of cyclooxygenase (COX-1 and COX-2).

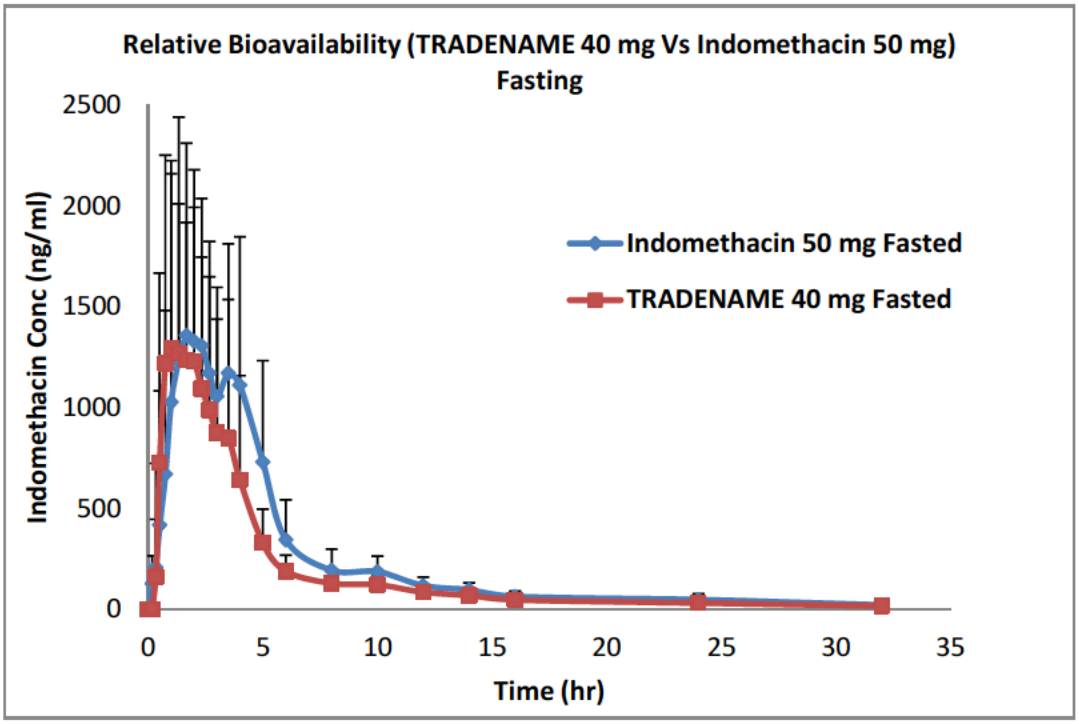
Pharmacokinetics

Two Phase 1 studies were submitted in support of this application, however only one of these studies was conducted with the commercial formulation. Because Indocin was discontinued and not available, the Applicant conducted a relative bioavailability study against indomethacin 50 mg IR capsules (ANDA 70624, Mylan Pharmaceuticals). The Division agreed with the Applicant during clinical development that this was the correct approach. Study IND1-12-07, a relative BA, dose-proportionality and food effect study, was reviewed in full because this study utilized commercial formulation. Study IND1-08-01 which used the proof of concept formulation, was not reviewed in full, however the food effect data for the reference drug in this study was reviewed by the team. The following is a summary of the findings taken from Dr. Naraharisetti' s review:

> **Relative bioavailability of TIVORBEX capsules compared to reference indomethacin IR capsules (ANDA 070624):**
> The relative BA of TIVORBEX 40 mg capsules was compared to indomethacin 50 mg capsules (ANDA 070624) under fasting conditions in 38 healthy subjects.
>
> - TIVORBEX 40 mg capsules does not result in similar systemic exposure as reference indomethacin 50 mg IR capsules and are not bioequivalent.
> - When taken under fasted conditions, 20% lower dose of TIVORBEX capsules (40 mg) compared to indomethacin IR capsules (50 mg) results equivalent (geometric mean) peak concentrations (Cmax) and 22 and 21 % lower (geometric mean) AUC_{0-t} and $AUC_{0-\infty}$, respectively. The median time to reach peak concentrations (Tmax) for TIVORBEX capsules is 21 minutes earlier compared to indomethacin capsules (TIVORBEX 1.67 hours versus indomethacin IR capsules 2.02 hours).
> - There were no differences in mean elimination half-life ($t_{1/2}$) between TIVORBEX capsules and indomethacin IR capsules (TIVORBEX 7.6 hours vs. indomethacin IR capsules 7.2 hours).

The relative BA of Tivorbex vs. indomethacin is shown in the table below from Dr. Naraharisetti' s review:

Figure 2.4.1a: Mean ± SD indomethacin plasma concentration-time profiles after administration of TIVORBEX capsules and indomethacin IR capsules under fasted conditions.



Dose Proportionality between 20 and 40 TIVORBEX capsules:

- (b) (4) The 20 and 40 mg strengths show dose proportional pharmacokinetics for Cmax and AUC under fasted conditions.

Food Effect on TIVORBEX and indomethacin IR capsules:

The food effect was assessed for TIVORBEX 40 mg capsules and indomethacin IR capsules were evaluated in 38 and 40 healthy subjects, respectively.

- When taken under fed conditions, TIVORBEX capsules results in food effect comparable to that of reference indomethacin capsules.
- Under fed conditions, TIVORBEX 40 mg capsules results in 46% and 9% lower Cmax and AUC (AUC_{0-t} and $AUC_{0-\infty}$), respectively compared to the fasted conditions. Taking TIVORBEX with food delayed the Tmax by 1.33 hours (~80 minutes) (1.67 hours fasted vs. 3.00 hours fed).
- Under fed conditions, the reference indomethacin IR 50 mg capsules (ANDA 070624) results in 49% lower Cmax and 19% lower AUC (AUC_{0-t} and $AUC_{0-\infty}$) compared to fasted conditions. Taking indomethacin IR capsules with food delayed the Tmax by 1.5 hr (~90 minutes) (2.00 hours

fasted vs 3.50 hours fed). The source of reference food effect data is from the study IND1-08-01 conducted by the Sponsor.

- The Indocin label does not have the food effect information. The observed food effect for TIVORBEX capsules is comparable to the reference indomethacin capsules and does not warrant labeling recommendations.

Biopharmaceutics

The Biopharmaceutics review focused on the evaluation and acceptability of the proposed dissolution methodology and the dissolution acceptance criteria. Both were found acceptable. The drug product dissolution data support the proposed drug product expiry date of 24 months when stored at 25 °C/60% RH.

6. Clinical Microbiology

This section is not applicable as Tivorbex is not an antimicrobial.

7. Clinical/Statistical- Efficacy

The efficacy portion of this NDA review was conducted by Anjelina Pokrovnichka, M.D., with secondary concurrence by me. The statistical review was conducted by Yan Zhou, Ph.D., with secondary concurrence by Janice Derr, Ph.D.

The Applicant submitted the results of two key Phase 3 trials (IND3-08-04b and IND3-10-06) as evidence of efficacy for Tivorbex for the treatment of mild to moderate acute pain. They also submitted the results of one Phase 2, proof-of-concept study (IND3-08-04b) as supportive evidence. The Phase 2 study was conducted using the proof-of-concept formulation rather than the commercial formulation, and therefore is not discussed in this review.

Drs. Pokrovnichka and Zhou conducted full reviews of the two Phase 3 trials, which are summarized below.

Phase 3 study design

The two phase 3 studies were essentially identical in design, except there was no active comparator group receiving celecoxib in Study IND3-10-06. Both studies were randomized, double-blind, multiple-dose, parallel-group, placebo-controlled studies of Tivorbex for the treatment of acute postoperative pain after bunionectomy. Subjects included in the studies were male or female patients between the ages of 18 and 65 years undergoing primary, unilateral, first metatarsal bunionectomy. They were required to have a pain intensity of at least 40 mm on a 100 mm visual analog scale (VAS) during the nine hour period after discontinuation of the anesthetic block. Subjects were excluded if they had any contraindication to NSAID use, clinically significant or unstable disease states, or were taking anticoagulants, corticosteroids, or opioids. Eligible subjects were randomly assigned, in a 1:1:1:1 ratio:

- Tivorbex capsules 40 mg TID
- Tivorbex capsules 40 mg BID
- Tivorbex capsules 20 mg TID
- Placebo
- *Celecoxib 200 mg BID (400 mg first dose) only in Study IND3-10-06*

Subjects whose pain was not adequately managed by study drug could receive one tablet of hydrocodone/acetaminophen 10 mg/325 mg orally every four to six hours as needed. If the hydrocodone/acetaminophen provided inadequate pain relief or was not tolerated, subjects could receive one tablet oxycodone/acetaminophen 7.5 mg/325 mg orally every six hours as needed. Total daily rescue could not exceed six tablets. Subjects were encouraged to wait at least one hour after the first dose of study drug to request rescue.

Efficacy assessments consisted of pain intensity (PI) measured using VAS (100 mm scale) at baseline, PI (VAS) and pain relief (PR) using 5-point categorical scale in inpatient diary at 15, 20, and 45 minutes, and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 16, 20, 24, 32, 40, and 48 hours, before the first use of rescue analgesia if before the 8-hour time point, and at premature study termination. Times to first perceptible and meaningful pain relief were measured using the double-stopwatch method, and patients global evaluation of study drug was measured at the end of treatment Day 3, before discharge from study site, or immediately prior to first dose of rescue medication, whichever occurred first.

The primary efficacy endpoint for both studies was the time-weighted sum of pain intensity difference from baseline over 48 hours after the first dose (VASSPID 48). The primary efficacy analysis utilized an analysis of covariance (ANCOVA) model with baseline pain score as a covariate and treatment as a factor. To control for multiplicity, a sequential testing procedure was applied for the comparisons of the three doses of Tivorbex with placebo in the following order:

1. Tivorbex 40 mg TID compared to placebo
2. Tivorbex 40 mg BID compared to placebo
3. Tivorbex 20 mg TID compared to placebo

In Study IND3-08-04b, there was no comparison made between Tivorbex and celecoxib in the primary analysis.

Secondary efficacy endpoints included VASSPID 24, time to onset of analgesia, time to first use of rescue medication, and total amount of rescue use during the 48 hours of treatment. None were identified by the Applicant as key secondary endpoints.

Missing pain assessments for subjects who discontinued early due to lack of efficacy, adverse event, or intolerance to study drug were imputed using baseline observation carried forward (BOCF). Missing pain assessments due to other reasons were imputed using last observation carried forward (LOCF). For subjects who took any dose of rescue medication, all scheduled pain assessments after the first dose of rescue were disregarded and imputed using BOCF.

As stated in Dr. Zhou's review:

> The applicant used a hybrid BOCF/LOCF method to impute pain scores after early discontinuation. In 2010, the National Academy of Science (NAS) released a report on missing data. The report does not recommend single imputation approach to impute missing values. Although the proposed BOCF/LOCF method is a single imputation method, I am not concerned about it as very few subjects discontinued early in each reviewed study.

Sensitivity analyses for the primary endpoint conducted by the Applicant included adding gender as a factor into the ANCOVA model, and post hoc analyses requested by the Agency conducted after unblinding of data that included limiting the BOCF imputation to four hours following each dose of rescue. The Mixed Model Repeated Measures (MMRM) method that used all available data rather than imputing missing pain scores, was conducted. In addition, the original protocol defined ANCOVA analysis was also repeated by Dr. Zhou.

Results

The demographic and baseline characteristics were similar for both studies and among treatment groups. The majority of subjects were white (72-76%) and female (83-85%) and the mean age was 40-41 years. The overall baseline pain intensity was 72-73 on a 100-mm VAS. The disposition of subjects in the two phase 3 studies was similar as shown in the tables below from Dr. Zhou's review. The dropout rate for both studies was quite low (≤ 3%).

In Study IND3-08-04b a total of 462 subjects were randomized, and all randomized subjects received at least one dose of study medication. A total of 373 subjects were randomized in Study IND3-10-06, and similarly, all subjects received at least one dose of study medication.

Table 2: Subject disposition in Study IND3-08-04b – Number (%) of Subjects

	Tivorbex			**Celecoxib**	**Placebo**
	40 mg TID	**40 mg BID**	**20 mg TID**		
Randomized	93	91	91	93	94
Completed	90 (97%)	88 (97%)	89 (98%)	93 (100%)	90 (97%)
Discontinued	3 (3%)	3 (3%)	2 (2%)		4 (3%)
Reason for discontinuation					
Lack of efficacy	1 (1%)	2 (2%)	2 (2%)		2 (2%)
Adverse event	2 (2%)	1 (1%)			2 (2%)

Table 8: Subject disposition in Study IND3-10-06 – Number (%) of Subjects

	Tivorbex			Placebo
	40 mg TID	40 mg BID	20 mg TID	
Randomized	94	93	92	94
Completed	92 (98%)	91 (98%)	90 (98%)	91 (97%)
Discontinued	2 (2%)	2 (2%)	2 (2%)	3 (3%)
Reason for discontinuation				
Lack of efficacy	1 (1%)		1 (1%)	3 (3%)
Adverse event		1 (1%)	1(1%)	
Lost to follow up	1 (1%)			
Investigator decision		1 (1%)		

The primary analyses for both studies are shown in the tables below from Dr. Zhou's review, and include the Applicant's analyses as well as Dr. Zhou's. She replicated the Applicant's primary analyses in both studies.

In Study IND3-08-04b, all three Tivorbex dosing regimens were superior to placebo in terms of the primary endpoint, although Tivorbex 40 mg BID is borderline significant. The results of the sensitivity analysis conducted by the Applicant that included gender as a factor is similar to the primary analysis.

Table 3: Primary Efficacy Analysis for Study IND3-08-04b (BOCF after the first rescue use)

	Applicant's Analyses					Reviewer's Analyses				
	Tivorbex			Celecoxib	Placebo	Tivorbex			Celecoxib	Placebo
	40 mg TID	40 mg BID	20 mg TID			40 mg TID	40 mg BID	20 mg TID		
N	93	91	91	93	94	93	91	91	93	94
LS Mean (SE)	510 (92)	328 (93)	381 (93)	279 (92)	68 (91)	510 (92)	328 (93)	380 (93)	279 (92)	67 (91)
Difference in LS mean (SE)	442 (130)	260 (130)	313 (130)	212 (130)		443 (130)	261 (130)	313 (130)	212 (130)	
95% CI for diff. in LS mean	(187, 697)	(4, 516)	(57, 569)	(-43, 466)		(188, 697)	(5, 517)	(57, 569)	(-43, 466)	
p-value for treatment effect	<0.001	0.046	0.017	0.103		0.0007	0.046	0.017	0.103	

For Study IND3-10-06, Dr. Zhou replicated the Applicant's results for the primary efficacy analysis. Only Tivorbex 40 mg TID and 40 mg BID were superior to placebo in terms of the primary efficacy endpoint.

Table 9: Primary Efficacy Analysis for Study IND3-10-06 (BOCF after the first rescue use)

	Applicant's Analyses				Reviewer's Analyses			
	Tivorbex			Placebo	Tivorbex			Placebo
	40 mg TID	40 mg BID	20 mg TID		40 mg TID	40 mg BID	20 mg TID	
N	94	93	92	94	94	93	92	94
LS Mean (SE)	599 (106)	623 (106)	343 (107)	281 (106)	598 (106)	623 (106)	343 (107)	281 (106)
Difference in LS mean (SE)	318 (150)	342 (150)	62 (150)		318 (150)	342 (150)	62 (150)	
95% CI for diff. in LS mean	(23, 612)	(47, 637)	(-234, 357)		(23, 612)	(47, 637)	(-233, 357)	
p-value for treatment effect	0.034	0.023	0.680		0.035	0.023	0.680	

In both Phase 3 studies, there was a very high percentage of subjects in each treatment group who used rescue medication at least once. The proportion of rescue use is smaller in the Tivorbex treatment groups compared to placebo. Although not depicted in the following tables, the time to use of first rescue was longer in the Tivorbex groups compared to placebo. Dr. Zhou created the following two tables that describe the use of rescue in each study.

Table 4: Rescue Use for Study IND3-08-04b

	Tivorbex			Celecoxib	Placebo
	40 mg TID	40 mg BID	20 mg TID		
Randomized	93	91	91	93	94
Subjects who took rescue within 48 hours	76 (82%)	82 (90%)	81 (89%)	83 (89%)	91 (97%)
Subjects who took rescue within first 8 hours	73 (78%)	78 (86%)	77 (85%)	81 (87%)	91 (97%)
Number of rescue use within first 24 hours					
mean (SD)	2.3 (1.7)	2.2 (1.4)	2.3 (1.7)	2.4 (1.6)	3.6 (1.7)
median	2	2	2	2	4
min, max	(0, 6)	(0, 5)	(0, 7)	(0, 6)	(0, 7)
Number of rescue use within 48 hours					
mean (SD)	2.7 (2.3)	2.7 (2.0)	3.0 (2.6)	3.1 (2.5)	5.0 (2.9)
median	2	2	2	3	5
min, max	(0, 9)	(0, 8)	(0, 12)	(0, 11)	(0, 13)

Table 10: Rescue Use for Study IND3-10-06

	Tivorbex			Placebo
	40 mg TID	40 mg BID	20 mg TID	
Randomized	94	93	92	94
Subjects who took rescue within 48 hours	75 (80%)	71 (76%)	80 (87%)	84 (89%)
Subjects who took rescue within first 8 hours	69 (73%)	67 (72%)	75 (82%)	81 (86%)
Number of rescue use within first 24 hours				
mean (SD)	1.6 (1.4)	1.9 (1.7)	2.1 (1.4)	3.0 (1.8)
median	1	1	2	3
min, max	(0, 6)	(0, 8)	(0, 6)	(0, 7)
Number of rescue use within 48 hours				
mean (SD)	1.9 (1.8)	2.4 (2.6)	2.7 (2.2)	4.2 (2.9)
median	1	1	2	4
min, max	(0, 9)	(0, 12)	(0, 12)	(0, 12)

The following summary from Dr. Zhou's review describes the use of rescue and subsequent sensitivity analyses conducted by Dr. Zhou and the Applicant. She concludes based on the sensitivity analyses, that all treatment regimens, including Tivorbex 20 mg TID are statistically superior to placebo in both studies.

> In Study IND3-08-04b, most arms had 89% or more subjects took rescue medications for pain management during the study. In Study IND3-10-06, most arms had 80% or more subjects took rescue medications for pain management during the study. When the percentage of subjects who take rescue medications is high, the approach to handling the pain scores after the rescue use may substantially influence the comparisons among treatment groups. In the applicant's primary analyses where all the pain scores after the first use of rescue medications were disregarded and replaced with the baseline pain scores, all Tivorbex treatment groups except Tivorbex 20 mg TID in Study IND3-10-06 were statistically significantly different from the placebo group. To evaluate the impact of the applicant's approach to handling pain scores after rescue use, I conducted additional sensitivity analyses in which the pre-rescue pain scores were carried forward to the next pain assessment (or pain assessments within a specified time window), if the pre-rescue pain scores were available. The applicant also conducted sensitivity analyses in which the pain scores within 4 hours after each dose of the rescue use were replaced with the baseline pain scores. All sensitivity analyses results were in favor of the active treatments including the lowest dose 20 mg TID. Since most of subjects used the rescue medications more than 1 time, the primary analysis is not reasonable as all pain scores after the first rescue

use were replaced by the baseline pain scores. Instead, the sensitivity analyses both I and the applicant conducted are more reasonable. Therefore, based on my review, I concluded that the two Phase 3 studies demonstrated the superiority of Tivorbex 20 mg TID, 40 mg BID and 40 mg TID over placebo in pain intensity reduction.

The sensitivity analyses for each study where the pain scores within four hours after each dose of rescue were replaced with the baseline pain scores are shown below from Dr. Zhou's review. All treatment groups in both studies demonstrated superiority over placebo.

Table 5: Sensitivity Analysis for Study IND3-08-04b (BOCF limited within 4 hours after each rescue use)

	Applicant's Revised Analyses					Reviewer's Analyses				
	Tivorbex			Celecoxib	Placebo	Tivorbex			Celecoxib	Placebo
	40 mg TID	40 mg BID	20 mg TID			40 mg TID	40 mg BID	20 mg TID		
N	90	88	88	93	90	93	91	91	93	94
LS Mean (SE)	2057 (87)	2127 (88)	1929 (88)	1838 (85)	1197 (87)	1988 (89)	2052 (90)	1905 (90)	1837 (89)	1149 (89)
Difference in LS mean (SE)	859 (123)	930 (123)	731 (123)	641 (122)		839 (126)	903 (126)	756 (126)	687 (126)	
95% CI for diff. in LS mean	(618, 1100)	(688, 1172)	(489, 974)	(402, 880)		(592, 1086)	(654, 1151)	(507, 1004)	(440, 934)	
p-value for treatment effect	<0.001	<0.001	<0.001	< 0.001		<0.001	<0.001	<0.001	< 0.001	

Source: Clinical Information Amendment Table 3.1.1-1 and Reviewer's Analyses

Table 11: Sensitivity Analysis for Study IND3-10-06 (BOCF limited within 4 hours after each rescue use)

	Applicant's Revised analyses				Reviewer's Analyses			
	Tivorbex			Placebo	Tivorbex			Placebo
	40 mg TID	40 mg BID	20 mg TID		40 mg TID	40 mg BID	20 mg TID	
N	93	91	90	91	94	93	92	94
LS Mean (SE)	2152 (88)	2107 (88)	1881 (89)	1393 (89)	2093 (93)	2068 (93)	1841 (94)	1352 (93)
Difference in LS mean (SE)	759 (125)	714 (125)	488 (125)		742 (131)	717 (132)	489 (132)	
95% CI for diff. in LS mean	(514, 1004)	(468, 961)	(241, 735)		(483, 1000)	(458, 975)	(230, 748)	
p-value for treatment effect	< 0.001	< 0.001	< 0.001		< 0.001	< 0.001	< 0.001	

Source: Clinical Information Amendment Table 3.2.1-1 and Reviewer's Analyses

Dr. Zhou's subgroup analysis of the primary endpoint by gender showed no statistically significant interaction between treatment and gender. No other subgroup analyses were conducted.

The secondary endpoints (pain relief, VASSPID 24, and patient global impression) generally

supported the results of the primary analysis in favor of the Tivorbex treatment groups compared to placebo. There were no important differences noted among the Tivorbex groups. Mean time to onset of analgesia for all Tivorbex groups was between 1.3 and 1.5 hours for all treatment groups in both studies.

I agree with Drs. Pokrovnichka and Zhou's conclusion that, despite the high percentage of rescue medication use, Tivorbex 40 mg TID, 40 mg BID, and 20 mg BID were more efficacious than placebo in the treatment of acute post-operative pain following bunionectomy.

8. Safety

Dr. Pokrovnichka conducted the review of safety. The following is a summary of key findings from her review. I will primarily discuss the findings from the pooled Phase 3 studies. There were no additional safety issues that were identified in the Phase 1 or 2 trials.

The Applicant was advised in pre NDA submission advice that at least 500 subjects must be exposed to Tivorbex during drug development in order to understand its safety profile. A total of 735 subjects received at least one dose of Tivorbex capsules in completed trials, including 80 healthy subjects in Phase 1 trials, 101 subjects in the Phase 2 trial, and 554 subjects in the Phase 3 trials. In general, Tivorbex was well tolerated when administered in single and repeated doses for up to 48 hours. No new safety concerns beyond those common to the NSAID class were identified.

The safety population consisted of all subjects who received at least one dose of Tivorbex. Data from the two Phase 3 trials were pooled, and data from the Phase 2 trial and two Phase 1 trials were presented individually. The extent of exposure in the Phase 3 trials is shown in the table below from Dr. Pokrovnichka's review. The majority of patients were exposed for at least 24 hours.

Exposure

	Tiforbex Capsules			
Exposure	**40 mg tid n=187**	**40 mg bid n=184**	**20 mg tid n=183**	**Combined n=554**
Time of Exposure, n (%)				
0 to 24 hours	3 (1.6)	4 (2.2)	4 (2.2)	11 (2.0)
≥24 hours	184 (98.4)	180 (97.8)	179 (97.8)	543 (98.0)
Cumulative Dose, n (%)				
<120 mg	3 (1.6)	4 (2.2)	4 (2.2)	11 (2.0)
120 mg	0	1 (0.5)	179 (97.8)	180 (32.5)
160 mg	1 (0.5)	179 (97.3)	0	180 (32.5)
240 mg	183 (97.9)	0	0	183 (33.0)

There we no deaths in any trial, and only one serious adverse event (SAE) occurred in a Phase 3 trial. The SAE was a deep vein thrombosis in a 40 year old woman on trial day 6, who was receiving ethinyl estradiol/desogestrel at the time of the event. It is unclear whether this event was associated with Tivorbex, however, the determination is confounded by the concurrent use of hormonal supplementation, and immobility following bunionectomy surgery.

A total of seven treatment emergent adverse events (TEAEs) were associated with subject discontinuation from the Phase 3 studies, five subjects received Tivorbex and two placebo. One event of angioedema and two events of urticaria occurred in the Tivorbex group. All events were coded as non-serious and mild to moderate in intensity. Other events in the Tivorbex group included one each of uvulitis and nausea.

A total of 626 (75%) of the safety population experienced at least one TEAE. The incidence across the Tivorbex treatment groups was similar ranging from 70-80%, and was similar to placebo. The table below from Dr. Pokrovnichka's review details the incidence of TEAEs by treatment group.

Table 1: Summary of Adverse Events (Integrated Safety Population)

Category, n (%)	Tiforbex Capsules				Celecoxib Capsules 200 mg[a] bid n=93	Placebo n=188	Total N=835
	40 mg tid n=187	40 mg bid n=184	20 mg tid n=183	Combined n=554			
Subjects with ≥1TEAEs	131 (70.1)	148 (80.4)	137 (74.9)	416 (75.1)	68 (73.1)	142 (75.5)	626 (75.0)
Subjects with ≥1 treatment-related TEAE	50 (26.7)	64 (34.8)	59 (32.2)	173 (31.2)	26 (28.0)	65 (34.6)	264 (31.6)
Subjects with ≥1 severe TEAE	3 (1.6)	0	2 (1.1)	5 (0.9)	0	0	5 (0.6)
Subjects with ≥1 serious TEAEs	0	1 (0.5)	0	1 (0.2)	0	0	1 (0.1)
Subject who terminated trial early due to AE	2 (1.1)	2 (1.1)	1 (0.5)	5 (0.9)	0	2 (1.1)	7 (0.8)
Subjects who died	0	0	0	0	0	0	0

(Source: Applicant's table from ISS, 2.7.4, page 32)

Dr. Pokrovnichka stated in her review:

> The most frequent TEAEs were nausea, post procedural edema, headache, dizziness, vomiting, post procedural hemorrhage, and constipation. Nausea was the most frequently reported event (282 subjects, 34%), with similar frequency across treatment groups. A slightly higher incidence of headache (16%) was reported in the Tivorbex Capsules 40 mg tid treatment group compared with placebo (11%). The incidence of headache in the Tivorbex Capsules 40 mg bid and 20 mg tid groups was comparable to that in the placebo group

The following table from Dr. Pokrovnichka's review details the incidence of TEAEs across treatment groups in the Phase 3 studies. Although the celecoxib group is included in the table, no claims can be made regarding comparative safety between Tivorbex and celecoxib. The Sponsor did not demonstrate that the dose of celecoxib used in the studies was of similar potency to the doses of Tivorbex, therefore there is no basis for a comparison of safety.

Only headache and dizziness appeared to occur at increased frequency with increased doses of Tivorbex. The other common TEAEs did not appear to have a dose response. However, this may reflect, in part, adverse events from the use of rescue medication.

Table 2: TEAEs occurring in more than 1% of combined Tivorbex Capsule subjects (Integrated safety Population)

Preferred Term, n (%)	Tiforbex Capsules				Celecoxib Capsule 200 mg[a] bid n=93	Placebo n=188	Total N=835
	40 mg tid n=187	40 mg bid n=184	20 mg tid n=183	Combined n=554			
Any TEAE	131 (70.1)	148 (80.4)	137 (74.9)	416 (75.1)	68 (73.1)	142 (75.5)	626 (75.0)
Nausea	62 (33.2)	60 (32.6)	63 (34.4)	185 (33.4)	30 (32.3)	67 (35.6)	282 (33.8)
Post procedural edema	44 (23.5)	40 (21.7)	48 (26.2)	132 (23.8)	25 (26.9)	60 (31.9)	217 (26.0)
Headache	29 (15.5)	25 (13.6)	20 (10.9)	74 (13.4)	5 (5.4)	21 (11.2)	100 (12.0)
Dizziness	28 (15.0)	26 (14.1)	18 (9.8)	72 (13.0)	7 (7.5)	32 (17.0)	111 (13.3)
Vomiting	14 (7.5)	19 (10.3)	21 (11.5)	54 (9.7)	3 (3.2)	21 (11.2)	78 (9.3)
Post procedural hemorrhage	9 (4.8)	20 (10.9)	9 (4.9)	38 (6.9)	8 (8.6)	11 (5.9)	57 (6.8)
Constipation	7 (3.7)	9 (4.9)	11 (6.0)	27 (4.9)	3 (3.2)	9 (4.8)	39 (4.7)
Pruritus	4 (2.1)	5 (2.7)	8 (4.4)	17 (3.1)	4 (4.3)	0	21 (2.5)
Diarrhea	4 (2.1)	6 (3.3)	4 (2.2)	14 (2.5)	0	1 (0.5)	15 (1.8)
Dyspepsia	6 (3.2)	3 (1.6)	1 (0.5)	10 (1.8)	3 (3.2)	1 (0.5)	14 (1.7)
Post procedural swelling	2 (1.1)	5 (2.7)	2 (1.1)	9 (1.6)	0	1 (0.5)	10 (1.2)
Presyncope	3 (1.6)	5 (2.7)	1 (0.5)	9 (1.6)	2 (2.2)	3 (1.6)	14 (1.7)
Rash	4 (2.1)	2 (1.1)	3 (1.6)	9 (1.6)	0	0	9 (1.1)
Abdominal pain upper	3 (1.6)	2 (1.1)	3 (1.6)	8 (1.4)	0	1 (0.5)	9 (1.1)
Somnolence	4 (2.1)	3 (1.6)	1 (0.5)	8 (1.4)	3 (3.2)	1 (0.5)	12 (1.4)
Erythema	2 (1.1)	2 (1.1)	2 (1.1)	6 (1.1)	1 (1.1)	10 (5.3)	17 (2.0)
Pruritus generalized	1 (0.5)	3 (1.6)	2 (1.1)	6 (1.1)	1 (1.1)	0	7 (0.8)

(Source: Applicant's table from ISS, 2.7.4, page 33)

Dr. Pokrovnichka stated:

> The majority of the TEAEs were mild (61%) or moderate (13%) in intensity. A total of 13 subjects reported severe TEAEs across all trials and 5 (0.6%) across the Phase 3 trials. The reported severe TEAEs included nausea, vomiting, alveolar osteitis, muscle tightness, and headache. No severe CV, GI, or renal TEAEs of the type reported in class labeling for NSAIDs (myocardial infarction, stroke, acute coronary syndrome, ulcers, GI bleeding, hypertension, renal failure, or renal insufficiency) were observed across the Tivorbex Capsules clinical trials.

There were no clinically important changes in vital signs in Phase 1 or 2 trials. As shown in the table below, in the Phase 3 trials, a slightly higher proportion of subjects in the Tivorbex treatment groups had at least one value of potential clinical concern (low and high) for diastolic and systolic BP compared to the placebo group. All blood pressure changes returned to near baseline at follow-up. There were no TEAEs reported as hyper- or hypotension in any subject who received Tivorbex, and there were no discontinuations or SAEs associated with changes in blood pressure. Additional information was requested of the Applicant including shift tables (for the worst percent change) for systolic and diastolic blood pressure for the Phase 3 safety population. For systolic and diastolic pressures, the ranges, mean changes, and percent change to worst value for all treatment groups and placebo were similar. Transient elevation of blood

pressure is a known adverse reaction associated with the use of NSAIDs, and review of the Tivorbex safety database did not reveal any unexpected findings in this regard.

Table 3: Summary of subjects with VS measurements of potential clinical concern (Phase 3 trials)

Category, n (%)	Tiforbex Capsules				Celecoxib Capsules 200 mg[a] bid n=93	Placebo n=188	Total N=835
	40 mg tid n=187	40 mg bid n=184	20 mg tid n=183	Combined n=554			
Systolic blood pressure							
High	62 (33.2)	52 (28.3)	51 (27.9)	165 (29.8)	27 (29.0)	48 (25.5)	240 (28.7)
Low	3 (1.6)	14 (7.6)	10 (5.5)	27 (4.9)	3 (3.2)	7 (3.7)	37 (4.4)
Diastolic blood pressure							
High	49 (26.2)	49 (26.6)	47 (25.7)	145 (26.2)	23 (24.7)	35 (18.6)	203 (24.3)
Low	40 (21.4)	50 (27.2)	44 (24.0)	134 (24.2)	26 (28.0)	35 (18.6)	195 (23.4)
Heart rate							
High	38 (20.3)	32 (17.4)	35 (19.1)	105 (19.0)	18 (19.4)	51 (27.1)	174 (20.8)
Low	15 (8.0)	9 (4.9)	8 (4.4)	32 (5.8)	5 (5.4)	9 (4.8)	46 (5.5)
Respiratory rate							
High	136 (72.7)	117 (63.6)	121 (66.1)	374 (67.5)	71 (76.3)	128 (68.1)	573 (68.6)
Low	0	0	1 (0.5)	1 (0.2)	0	1 (0.5)	2 (0.2)
Oral body temperature							
High	52 (27.8)	46 (25.0)	43 (23.5)	141 (25.5)	17 (18.3)	75 (39.9)	233 (27.9)
Low	125 (66.8)	124 (67.4)	116 (63.4)	365 (65.9)	56 (60.2)	116 (61.7)	537 (64.3)

Laboratory evaluations and ECGs were conducted only at baseline in the clinical trials.

I concur with Dr. Pokrovnichka's conclusion that Tivorbex was generally well tolerated in the clinical trials, and there were no new or unusual safety signals detected. The Tivorbex label will include all safety language common to the NSAID class, including the box warning, contraindications, warnings, drug-drug and drug-disease interactions, and special populations.

9. Advisory Committee Meeting

An Advisory Committee meeting was not convened for this NDA.

10. Pediatrics

No studies of Tivorbex have been conducted in pediatric patients. Because Tivorbex represents a new indication for indomethacin, the Pediatric Research and Equity Act (PREA) is triggered, and pediatric studies are required for this product.

The Applicant submitted a pediatric study plan with this submission that was not consistent with advice provided by the Division at the EOP2 meeting. At that time the Division informed the Applicant that studies would need to be conducted throughout the entire pediatric age range, and an age appropriate formulation must be developed for patients who could not take the adult formulation. The Applicant was also informed that efficacy may be extrapolated

from adults to pediatric patients two years of age and older for NSAIDs, consistent with the Division's current policy.

The pediatric plan submitted with the NDA included a request for a waiver of studies in pediatric patients (b) (4) and a deferral for subjects (b) (4) During the review cycle the Applicant was informed that the pediatric study plan may include a waiver request for studies in pediatric patients under 1 year of age that included a justification for the waiver, and a deferral for studies in patients 2 to <6 years and 6 to 17 years. The waiver request for patients less than one year was based on the reason that the product does not represent a meaningful therapeutic benefit over existing therapies and is unlikely to be used in a substantial number of patients in this age group. This rationale was substantiated by reviews conducted by the Pediatric and Maternal Health Staff[1] (PMHS) regarding a recommendation for a lower age range for studies of indomethacin in the pediatric age group, and the Division of Epidemiology II on the use of indomethacin in the pediatric population (which is quite low)[2]. The deferral request was based on the reason that the product is ready for approval in adults.

The following are the studies required under PREA, and timeline 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 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] Snyder, Donna; Sachs, Hari; "Memorandum to file: input on appropriate lower age limit for PREA PMR studies of NSAIDS indicated for acute pain," DARRTS October 24, 2013, NDA 204592 (Zorvolex) and NDA 204768 (Tivorbex)
[2] Ready, Travis; Mehta Hina; Governale, Laura: Drug utilization review pediatric patients, indomethacin; DARRTS October 18, 2013, NDA 204768

Timeline for Pediatric Studies

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 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
- 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 also 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.

12. Labeling

- The Division of Medication Error Prevention and Analysis (DMEPA) conducted a review, submitted to DARRTS January 3, 2014, of the proprietary name Tivorbex, and found it acceptable from a safety and promotional perspective. This was the second proprietary name to be reviewed under this application. The first was (b) (4) which was withdrawn by the Applicant on September 4, 2013 after DMEPA informed the Applicant that (b) (4) which is not acceptable.

- DMEPA also reviewed carton and container labels and the package insert (review in DARRTs January 8, 2014), and provided recommendations for label revision from the medical error perspective. The Applicant accepted all of the recommendations.

- Because bioequivalence was not demonstrated for Tivorbex and oral indomethacin capsules, the Tivorbex label will include a statement that Tivorbex and indomethacin capsules are not interchangeable on a mg for mg basis, and should not be substituted for one another..

- The Pediatric and Maternal Health Staff (PMHS) were consulted to provide input regarding sections of the label related to nursing mothers and pregnancy. They reviewed and summarized published data on indomethacin use during pregnancy and lactation in their review dated January 27, 2014, and recommended language to be included in Sections 5 Fetal Toxicity, 5.10 Pregnancy Fetal Toxicity, 8.1 Pregnancy, 8.3 Nursing Mothers, and 17,1 Fetal Toxicity. Their recommended language has been incorporated into the Tivorbex label.

- The Office of Prescription Drug Promotion (OPDP) reviewed the package insert, Medication Guide, and carton/container labels, and provided input regarding unsupported promotional language. OPDP's recommendations were incorporated into the labeling.

- The Tivorbex label will include all NSAID class language, including the Box Warning, and the NSAID class Medication Guide.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

  Approval

- Risk Benefit Assessment

  The Applicant developed Tivorbex as a new, immediate-release formulation of indomethacin to "address the need for lower-dose indomethacin options for the treatment of mild to moderate acute pain." Tivorbex capsules contain 20% less of the active ingredient compared to the previously approved oral indomethacin products. The Applicant maintains that the manufacturing technology used to reduce the indomethacin drug substance particle size in Tivorbex will enhance the rates of dissolution (b) (4) However, the previously approved indomethacin capsules are 100% bioavailable following oral administration and time to peak concentration is approximately two hours. While the mean time to reach peak concentrations for Tivorbex capsules is 21 minutes earlier than the comparator indomethacin capsules, (1.7 hrs vs 2.0 hrs), under fasted conditions, the systemic exposure to Tivorbex is approximately 20% lower than the comparator, and the clinical significance of the earlier Tmax is not known because the Applicant did not conduct any comparative studies between Tivorbex and indomethacin capsules in order to make comparative safety or efficacy claims or to substantiate their rationale for the product.

  However, the Applicant did demonstrate evidence of efficacy on the primary endpoint, VASSPID 48, for Tivorbex in two adequate and well-controlled clinical trials in patients with postoperative bunionectomy pain. Subjects were required to have a pain intensity rating of at least 40-mm on a 100-mm visual analog scale (VAS) to enter the study, which is generally considered at least moderate pain. In

both studies the vast majority of subjects required rescue medication in all treatment groups, with only a slightly greater proportion of placebo subjects requiring rescue compared to Tivorbex-treated patients. Based on these results, the study population appears reasonable to support the proposed indication (i.e., treatment of mild-moderate acute pain in adults). Both studies support the efficacy of the three proposed dosing regimens of Tivorbex 40 mg BID, 40 mg TID, and 20 mg TID.

The Applicant provided adequate subject exposure to Tivorbex, and its safety profile appears similar to other NSAIDs. No new or unexpected safety signals were detected during review of the safety database.

The results of the clinical trials, along with the Agency's previous findings of safety and efficacy for the reference product (Indocin) provide adequate evidence that the benefit/risk balance is in favor of approval for this product. The product label will include all NSAID class language including the Box Warning, as well as language specific to Tivorbex. In addition, the NSAID class Medication Guide must be part of this approval.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

None

- Recommendation for other Postmarketing Requirements and Commitments

The following pediatric studies are required under PREA

- Study 1: An open-label pharmacokinetic and safety study or studies of an age appropriate formulation of indomethacin in pediatric patients 6 through 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

- 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/

ELLEN W FIELDS
02/03/2014