CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204768Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA: 204768	Submission Date: 04/30/2013
Relevant IND(s):	101940
Submission Type; Code:	505 (b) (2)
Reference Drug:	Indocin capsules (NDA 016059)
Brand Name:	TIVORBEX capsules
Generic Name:	Indomethacin
Formulation; Strength(s):	Immediate-release capsules; 20 and 40 mg
Clinical Pharmacology Reviewer:	Suresh B Naraharisetti, Ph.D.
Team Leader:	Yun, Xu, Ph.D.
OCP Division:	Division of Clinical Pharmacology II
OND Division:	Anesthesia Analgesia and Addiction Products
Sponsor:	Iroko Pharmaceuticals, LLC
Proposed Indication:	Treatment of mild to moderate acute pain in adults
Proposed Dosage Regimen:	20 mg TID or 40 mg BID or TID

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1.0 Executive Summary

1.1 Recommendation

From the Clinical Pharmacology perspective, NDA 204768 submitted on 04/30/2013 is acceptable provided an agreement can be reached between the sponsor and the Agency regarding the language in the package insert.

1.2 Phase 4 Commitments

None

1.3. Summary of Clinical Pharmacology Findings

Iroko Pharmaceuticals, LLC submitted a 505 (b) (2) application for TIVORBEX capsules, an immediate-release (IR) formulation of Indomethacin for the treatment of mild to moderate acute pain in adults. As a 505(b) (2) NDA, the applicant conducted two Phase 3 trials in bunionectomy patients using the to-be-marketed formulation, in conjunction with the Agency's previous findings of safety and efficacy for the reference drug Indocin (NDA 016059). Currently, the Indocin NDA was discontinued and the Federal Register determination is that, it was not discontinued or withdrawn for safety or efficacy reasons. Since the reference drug Indocin was discontinued, for establishing the clinical bridge, Iroko conducted a relative bioavailability (BA) against indomethacin 50 mg IR capsules of ANDA 070624 (Mylan Pharmaceuticals, Inc). This approach for conducting a relative BA study with ANDA 070624 was agreed during meetings with sponsor before NDA filing (DARRTS 11/14/2012 meeting minutes).

The dose strengths for TIVORBEX oral capsules are 20 and 40 mg (b) (4) The sponsor proposed dosing regimen for 20 mg strength is three times daily (TID) and for 40 mg strength is two times daily (BID) or TID. The proposed TID dosing regimen for 20 mg strength is different compared reference Indocin 25 mg capsules, which can be dosed BID or TID. The dosing regimen for 40 mg strength is BID or TID, similar to reference Indocin 50 mg capsules.

Indomethacin (Indocin) IR oral capsules were originally approved on June 10, 1965. Since then other formulations of such as extended release capsules, injection, suspension and rectal suppositories have been approved. The proposed TIVORBEX capsules are a reformulation of indomethacin with reduced particle size. The TIVORBEX capsules contain 20 mg or 40 mg of indomethacin as the sole analgesic ingredient, representing a 20% lower indomethacin dose compared to reference Indocin (25 mg and 50 mg). The 20% lower dose calculation of 20 mg and 40 mg TIVORBEX capsules was made (b) (4) Sponsor's rationale of reduced particle size is to increase the surface area to-mass ratio (b) (4) This Sponsor has an approval for Zorvolex capsules (Diclofenac) with the similar rationale. With regard to improving of absorption / bioavailability of the proposed product; for reference drug indocin immediate release capsules, the peak concentrations (Cmax) of indomethacin appear at 2 hours (Tmax) and the bioavailability (BA) of indomethacin after oral administration is

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almost 100%, with 90% absorbed within 4 hours. Therefore, there may be little room for a new formulation to improve on the absorption in terms of Tmax of the drug.

For this NDA, the safety, the end of Phase 2, the pre-NDA meetings were held on 02/25/2009, 06/08/2010 and 10/23/2012, respectively under IND 101940. The clinical development program includes two clinical pharmacology studies and three clinical studies.

Clinical Pharmacology Studies:
Two clinical pharmacology studies, IND1-08-01 and IND1-12-07 were conducted for this application. Out of these two studies, IND1-08-01 was conducted with initial proof of concept formulation and hence not reviewed, expect for the food effect data of reference ANDA indomethacin IR capsules (A070624). The study IND1-12-07 was conducted with commercial scale formulation that fulfills the clinical pharmacology information of the proposed product from regulatory requirement perspective.

Phase 1 Study IND1-12-07 (with commercial scale formulation):

- Relative bioavailability (BA), dose-proportionality and food effect study.

Clinical Studies:
Sponsor conducted one Phase 2 and two Phase 3 clinical studies. The Phase 2 study, IND2-08-03 was conducted with initial proof of concept formulation. The two pivotal Phase 3 studies, IND3-08-04b and IND3-08-06 conducted commercial scale formulation serves for assessing the clinical safety and efficacy for this product.

Phase 2 studies (with proof- of concept formulation):

- IND2-08-03: Single dose study conducted in patients following surgical removal of impacted third molars. This study was conducted with a POC formulation and hence only serves as support to efficacy and safety.

Phase 3 Studies (with commercial scale formulation):

- IND3-08-04b (Phase 3 study): Multiple dose, pivotal safety and efficacy study in patients with acute postoperative pain following bunionectomy.
- IND3-08-06 (Phase 3 study): Multiple dose, parallel group, placebo controlled pivotal safety and efficacy study in patients with acute postoperative pain following bunionectomy.

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).

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- 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).

Dose Proportionality between 20 and 40 TIVORBEX capsules:

- [redacted] (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.

Overall, adequate information has been provided characterizing the clinical pharmacology aspects of TIVORBEX capsules.

2.0 Question Based Review

2.1 General Attributes of the Drug

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the the drug substance, and the formulation of the drug product?

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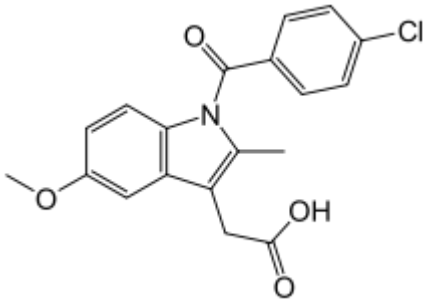
Table 2.1.1: Physical-Chemical Properties of Indomethacin Acid	
Drug Name	Indomethacin
Chemical Name	2-{1-[(4-chlorophenyl)carbonyl]-5-methoxy-2-methyl-1*H*-indol-3-yl}acetic acid
Structure	
Molecular Formula	C19H16ClNO4
Molecular Weight	357.79

Formulation:
TIVORBEX capsules are a reformulation of indomethacin with reduced particle size. TIVORBEX capsules are 20% lower in indomethacin dose compared to Indocin capsules. The two strengths of TIVORBEX capsules are 20 mg and 40 mg compared to the 25 mg and 50 mg strengths of Indocin.

2.1.2. What is the regulatory history of Indomethacin products?
Indomethacin is an approved drug that is already available and marketed in the United States as a treatment for multiple indications as shown in Table 2.1.2.

Table 2.1.2: Oranage Book Indomethacin products:

Drug name and Application #	Dosage form/Route	Strength	Company
Indomethacin 18-851	Capsule; oral	25 mg and 50mg	HERITAGE PHARMS INC
Indomethacin 18-858 70-624	Capsule; oral	25mg and 50mg	MYLAN
Indomethacin 22-536	Injectable	EQ 1mg base/vial	FRESENIUS KABI USA
Indomethacin 78-713	Injectable	EQ 1mg base/vial	BEDFORD
Indomethacin 70-673 70-674 74-464	Capsule; oral	25mg 50mg 75mg ER	SANDOZ
Indomethacin 70-719 70-756	Capsule; oral	25mg 50mg	IVAX SUB TEVA PHARMS
Indomethacin	Suppository; rectal	50mg	G AND W LABS

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73-314			
Indomethacin 79-175	Capsule; oral	75mg ER	AVANTHI INC
Indomethacin 91-549	Capsule; oral	75mg ER	AMNEAL PHARMS
Indomethacin 200-529	Capsule; oral	75mg ER	PADDOCK LLC
Indomethacin 201-807	Capsule; oral	75mg ER	HETERO LABS LTD III
Indomethacin 90-403	Capsule; oral	Multiple Strengths	ZYDUS PHARMS USA INC
Indomethacin 91-240	Capsule; oral	Multiple Strengths	HETERO LABS LTD III
Indomethacin 91-276	Capsule; oral	Multiple Strengths	GLENMARK GENERICS
Indomethacin 91-401	Capsule; oral	Multiple Strengths	CARACO

2.1.3 What is the composition of the to-be-marketed formulation of TIVORBEX capsules?

The proposed commercial dosage forms of TIVORBEX capsules include 20 mg and 40 mg strengths of Indomethacin acid. Table 2.1.3 provides the quantitative composition for both capsule strengths and the function of each component.

Table 2.1.3: Composition of TIVORBEX capsules 20 and 40 mg strengths

Component	**Quality Standard**	**Function**	**Strength**	
			20	**40**
			Amount per Capsule (mg/capsule weight)	**Amount per Capsule (mg/capsule weight)**
Indomethacin, USP	(b) (4)	Active pharmaceutical ingredient	20	40.0
Lactose monohydrate	NF	(b) (4)		
Microcrystalline cellulose	NF			
Croscarmellose sodium	NF			
Sodium lauryl sulfate	NF			
Sodium stearyl fumarate	NF			
Total capsule fill weight	-			

NF - National Formulary, USP = United States Pharmacopeia

(b) (4) capsule with a blue body with “IP-201” imprinted in white ink and a light blue cap with “20 mg” printed in white ink.

$ (b) (4) capsule with a blue body with “IP- 202” imprinted in white ink and a blue cap with “40 mg” printed in white ink

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2.1.4 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Indomethacin is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of Indomethacin, like that of other NSAIDs, is not completely understood but may be related to regulation of prostaglandin synthesis via prostaglandin synthetase. The mechanism involves an inhibition of cyclooxygenase (COX-1 and COX-2) pathways. The proposed indication for TIVORBEX capsules is for treatment of mild to moderate acute pain in adults.

2.1.5 What are the proposed dosage and route of administration?

TIVORBEX capsules are intended for oral administration. The proposed dosage is 20 mg TID or 40 mg BID or TID orally.

2.1.6 What are the core studies submitted in this NDA?

The clinical development program includes one pivotal clinical pharmacology study and one clinical safety and efficacy study.

- **IND1-12-07** (Phase 1 study using commercial scale formulation): Relative BA, dose proportionality and food effect study. This study is a randomized, single-dose, four-way crossover, relative bioavailability study of TIVORBEX capsules 20 mg and 40 mg and Mylan Indomethacin® 50 mg capsules, in healthy subjects under fasting conditions. This study fulfills the clinical pharmacology requirements of the proposed product.
- IND3-08-04b (Phase 3 study using commercial scale formulation): Multiple dose, pivotal safety and efficacy study in patients with acute postoperative pain following bunionectomy.
- IND3-08-06 (Phase 3 study using commercial scale formulation): Multiple dose, parallel group, placebo controlled pivotal safety and efficacy study in patients with acute postoperative pain following bunionectomy.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The clinical efficacy studies, IND3-08-04b and IND3-08-06 for treatment of acute postoperative pain after bunionectomy and the clinical pharmacology study characterizing the formulation form the basis to support the dosing for this NDA.

For final assessment of the safety and efficacy findings, see Clinical review by Dr. Anjelina Pokrovnichka (reviewing Medical Officer). Following is a brief summary of the Clinical Efficacy and Safety assessments provided by Dr. Anjelina Pokrovnichka.

Benefits:

The review of efficacy focused on two Phase 3 trials, IND3-08-04b and IND3-10-06. The third molar extraction Phase 2 trial, IND2-08-03, considered to provide only supportive

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data is not reviewed in detail. The review of safety focused on data from the two Phase 3 bunionectomy trials that were pooled and contributed most of the safety data.

- Evidence of effectiveness was established for Tivorbex Capsules 40 mg bid and 40 mg tid doses in two placebo-controlled Phase 3 trials using the pre-specified analysis for the primary endpoint, VAS summed pain intensity difference (VASSPID) over 0 to 48 hours. These results were confirmed by a series of sensitivity analyses to account for the use of rescue medication and to utilize different strategies for imputation of missing data. Evidence of effectiveness was established for the Tivorbex Capsules 20 mg tid dose in one of the Phase 3 trials using the prespecified analysis of the primary endpoint, but all of the sensitivity analyses were positive for this dose in both Phase 3 trials.
- The primary efficacy analysis is further supported by results in favor of Tivorbex Capsules on various secondary endpoints.
- Indomethacin is a well-established analgesic and this dosage form offers an additional treatment option for patients with mild to moderate acute pain

Risks:

- No new safety signal was identified in review of this application.
- The most commonly reported adverse events were nausea, post procedural edema, headache, dizziness, vomiting, post procedural hemorrhage, and constipation, with similar frequency across all active treatment groups.

Overall, the risk-benefit profile of Tivorbex Capsules in this population is favorable.

2.2.2 What efficacy and safety information (e.g., biomarkers, surrogate endpoints, and clinical endpoints) contribute to the assessment of clinical pharmacology study data? How was it measured?

No biological biomarker was assessed in this NDA. In two placebo-controlled studies the primary endpoint was VAS summed pain intensity difference (VASSPID) over 0 to 48 hours.

2.2.3. What are the general PK characteristics of the drug?

The absorption, distribution, metabolism, and excretion of Indomethacin as a molecular entity are described in the label for the reference listed drug (Indocin Label).

2.2.4 Were the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Indomethacin analgesic activity is primarily due to the parent compound Indomethacin; only the parent compound was measured to assess the PK parameters.

2.2.5. What are the characteristics of drug absorption? Are TIVORBEX parameters dose proportional?

From the Indocin package insert, it is known that indomethacin is 90% absorbed within 4 hours with peak concentrations appearing at 2 hour. The bioavailability of indomethacin after oral administration is almost 100% (per Indocin label).

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Dose-proportionality of TIVORBEX Capsules:
The dose proportionality between two strengths, 20 and 40 mg TIVORBEX capsules was assessed as part of study IND1-12-07 under fasted conditions. (b) (4)

Treatments:

- TIVORBEX capsules 20 mg Fasted (Batch # L0307815)
- TIVORBEX capsules 40 mg Fasted (Batch # L0307818)

The mean ± SD concentration-time profiles and PK parameters for 20 and 40 mg TIVORBEX capsules are shown in the Figures 2.2.5 and Table 2.2.5a, respectively. The dose proportionality for dose normalized indomethacin plasma PK parameters (40 mg vs. 20 mg) is shown in the Table 2.2.5b. The dose normalized PK parameters show that 20 and 40 mg TIVORBEX capsules results in dose proportional pharmacokinetics for Cmax and AUC under fasted conditions

Figure 2.2.5. Mean (± SD) of plasma concentration-time profiles after single dose administration of TIVORBEX 20 and 40 mg under fasted conditions.

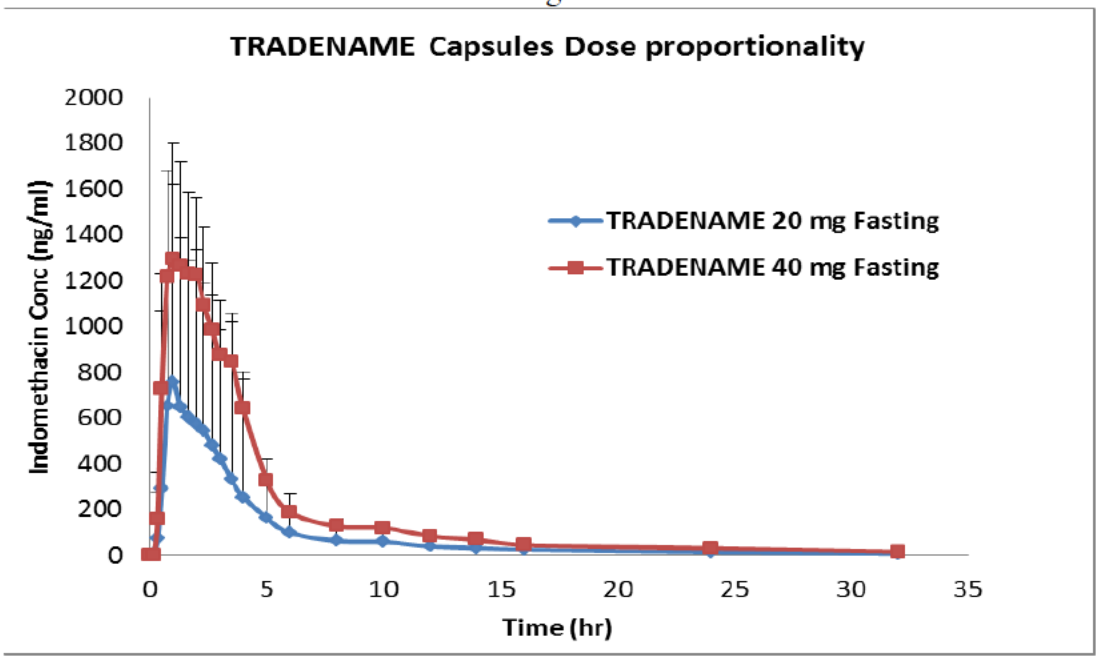

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Table 2.2.5a: PK parameters for TIVORBEX 20 and 40 mg dose strengths under fasted conditions.

Parameter	**TIVORBEX® 20 mg Arithmetic mean ± SD**	**TIVORBEX® 40 mg Arithmetic mean ± SD**
Cmax (ng/mL)	1165.9 ± 367.17	2368.8 ± 631.4
AUC_{0-t} (hr*ng/mL)	2844.8 ± 604.3	5924.8 ± 1467.1
$AUC_{0-\infty}$ (hr*ng/mL)	2981.8 ± 548.7	6110.1 ± 1393.2
Tmax (hr)*	1.67 (0.50 – 5.00)	1.67 (0.50 – 3.52)
T1/2 (hr)	8.13 ± 3.43	7.62 ± 3.26
Tlast (hr)[#]	28.0 ±4.04	29.8 ± 3.64
Clast (ng/mL)[φ]	10.54 ± 4.02	16.83 ± 14.99

*Median (min-max); [#]Tlast- Time for last observed concentration; [φ]Clast- last observed concentration

Table 2.2.5b: Dose proportionality for dose normalized indomethacin plasma PK parameters for 40 mg versus 20 mg.

Parameter	**Geometric LS mean ratio (40 mg / 20 mg)**	**90% CI of ratio**
Cmax (ng/mL)	1.038	0.944, 1.140
AUC_{0-t} (hr*ng/mL)	1.036	1.003, 1.070
$AUC_{0-\infty}$ (hr*ng/mL)	1.018	0.984, 1.052

2.3. Intrinsic factors

2.3.1. What is the pediatric plan?

TIVORBEX is a capsule formulation and this application triggers PREA because it is a new dosage form. For pediatric studies, Sponsor requested for a 'waiver' (b) (4) and 'deferral' for of pediatric studies (b) (4) however it is not acceptable to the Division.

Below is the pediatric studies requirement for this application, based on the discussion with Pediatric Review Committee (PeRC), on 1/15/2014

- Partial waiver in pediatric patients aged birth to < one year
  - Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients of this age and is not likely to be used in a substantial number of pediatric patients in this age group.

    - Justification of waiver for age group birth to less than 1 year (Source PERC documents): Indomethacin has been approved since 1965. Indomethacin is approved in an IV form, "to close a hemodynamically significant patent ductus arteriosus in premature infants weighing between 500 and 1750 g when after 48 hours usual medical management is ineffective." Indomethacin may be used off-label in patients with Juvenile Idiopathic Arthritis (JIA) and to treat certain uncommon headache disorders such as paroxysmal hemicrania and hemicrania continua. 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.

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Literature review did not support use in pediatrics for the acute pain indication proposed by the sponsor.

- A consult to evaluate the use of indomethacin in patients (b) (4) 0 to less than 1 year of age was requested from the Division of Epidemiology II (DEPI II). The review of use data of indomethacin in the pediatric population confirmed that use of indomethacin in pediatric patients is extremely low.
- DEPI II evaluated the extent of oral indomethacin use in pediatric patients aged less than 1, 1, 2-5, 6-11, and 12-16, and 17+ years, for years 2008 through 2012, and year-to-date August 2013 (b) (4)
- A Pediatric and Maternal Health Staff (PMHS) consult was requested to provide input on the appropriate lower age limit for PREA PMR studies of NSAIDs indicated for acute pain. PMHS recommended that the determination for waivers for a specific pediatric age group should be product specific and not generalized across the entire class of NSAIDs. Waiver requests for children less than one year of age, based on the grounds of unsafe use due to CYP2C9 immaturity, would generally not be accepted. Several drugs metabolized through CYP2C9 pathway are approved or being studied for use in children less than one year of age. The need for a waiver should be based on whether there is a public health benefit to performing the studies. If substantial use is demonstrated, then studies are particularly critical in the pediatric population where the product is expected to be used to inform dosing and to evaluate the adverse event profile in that specific age group. In the case of indomethacin, a literature review and DEPI II review of use data suggest that indomethacin is not typically used for the treatment of acute pain in the pediatric patients less than one year of age and does not represent a meaningful therapeutic benefit over existing therapies. Thus, indomethacin may qualify for a partial waiver in this age group.
- Based on the information provided above, a waiver is requested for the age group birth to <1 year, on the grounds that the product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is unlikely to be used in a substantial number of the pediatric age group for which a waiver is being requested.

- Deferral for pediatric patients aged 1 to < 17 years. Required pediatric studies as below:
  - Study 1: An open-label PK and safety study or studies of an age appropriate formulation of Indomethacin in pediatric patients 6 to < 17 years of age with acute mild or moderate pain.
  - Study 2: An open-label PK and safety study or studies of an age appropriate formulation of Indomethacin in pediatric patients 2 to < 6 years of age with acute mild or moderate pain.
  - Study 3: A PK, safety, and efficacy study or studies of an age appropriate formulation of Indomethacin in pediatric patients 1 to < 2 years of age with acute mild or moderate pain.

Reviewer comments:

This application was discussed at a meeting of the Pediatric Review Committee (PeRC) on January 15, 2014. The PeRC agreed with the Division to grant a partial waiver in

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pediatric patients aged birth to less than one year because 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 pediatric age group. The PeRC agreed with the Division on the proposed studies in pediatric patients aged 1 to less than 17 years, and to grant a deferral in this age range because the product is ready for approval in adults. PeRC requested a revised timeline to accelerate the protocol submissions. A request was sent to Sponsor to provide a new timeline that includes earlier dates for all protocol submissions, and adjusted study conduct dates and report submissions to align with those dates.

2.4. General Biopharmaceutics

2.4.1. What is the relative bioavailability of TIVORBEX® capsules compared to the reference drug, Mylan Indomethacin Capsules?

The relative bioavailability of TIVORBEX® 40 mg capsules was compared to reference Indomethacin 50 mg Capsules (Mylan ANDA) under fasted conditions as a part of study IND1-12-07. This study was done using commercial scale formulation of TIVORBEX. A total number of 40 healthy subjects completed the treatments.

Treatments:

- Test TIVORBEX capsules 20 mg (Batch # L0307815) Fasted
- Test TIVORBEX capsules 40 mg (Batch # L0307818) Fasted
- Test TIVORBEX capsules 40 mg (Batch # L0307818) Fed
- Reference Indomethacin IR capsules 50 mg (A070624) (Batch # 3037950)Fasted

There was at least a 7-day washout interval between doses. Blood samples for PK were collected for 32 hours after dosing.

Results:

The plasma concentration-time profiles comparing TIVORBEX 40 mg capsules and indomethacin 50 mg IR capsules under fasted conditions are shown in figures 2.4.1. The corresponding PK parameters are shown in Table 2.4.1a. The geometric mean ratios and the 90% CIs for AUC_{0-t} and $AUC_{0-\infty}$ and Cmax are shown in the Table 2.4.1b. The summary of results is shown below:

- 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 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 elimination half-life ($t_{1/2}$) between TIVORBEX capsules and indomethacin IR capsules (TIVORBEX 7.6 hours vs. indomethacin IR capsules 7.2 hours).

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

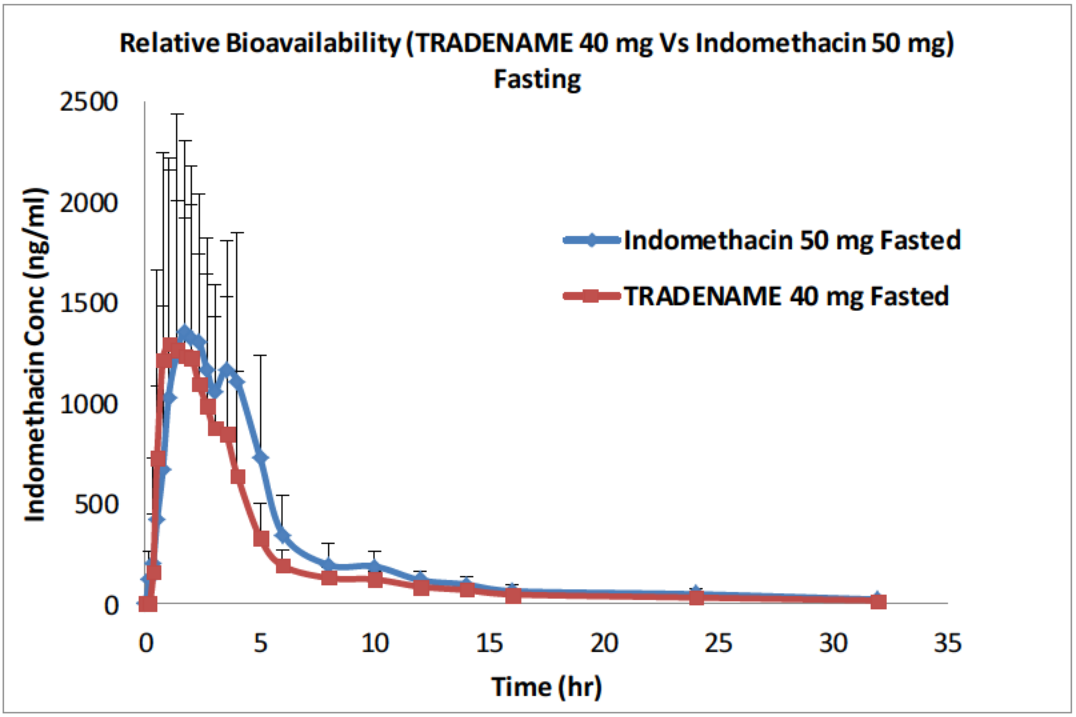

Table 2.4.1a. Pharmacokinetic parameters comparing TIVORBEX and indomethacin IR capsules under fasted conditions.

Parameter Arithmetic mean ± SD	**TIVORBEX capsules (40 mg) Fasted**	**Indomethacin IR capsules (50 mg) Fasted**
Cmax (ng/mL)	2368.8 ± 631.4	2369.40 ± 969.06
AUC_{0-t} (hr*ng/mL)	5924.8 ± 1467.1	7658.12 ± 1905.64
$AUC_{0-\infty}$ (hr*ng/mL)	6110.1 ± 1393.2	7762.16 ± 1845.52
Tmax (hr)*	1.67 (0.50 – 3.52)	2.02 (0.50 – 5.00)
T1/2 (hr)	7.62 ± 3.26	7.22± 2.43
Tlast (hr)[#]	29.8 ± 3.64	30.7 ± 3.53
Clast (ng/mL)[φ]	16.8 ± 15.0	22.2 ± 19.0

*Median (min-max); [#]Tlast- Time for last observed concentration; [φ]Clast- last observed concentration

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Table 2.4.1b: Geometric LS mean ratios and 90% confidence intervals for Cmax AUC_{0-t} and $AUC_{0-\infty}$ of TIVORBEX versus indomethacin IR capsules in fasted conditions.

Parameter	**Geometric LS mean**		**Geometric LS mean ratio (90% CI of ratio) [TIVORBEX 40 mg / Indomethacin IR 50 mg]**
	TIVORBEX capsules (40 mg)	**Indomethacin IR capsules (50 mg)**	
Cmax (ng/mL)	2292.60	2216.38	1.034 (0.908, 1.179)
AUC_{0-t} (ng.h/mL)	5832.63	7466.33	0.781 (0.755, 0.809)
$AUC_{0-\infty}$ (ng.h/mL)	6007.71	7646.23	0.786 (0.758, 0.815)

2.4.2 What is the effect of food on the BA of TIVORBEX in comparison to the indomethacin IR capsules?

For TIVORBEX capsules food effect was evaluated as part of the study IND1-12-07. This study was done using commercial scale formulation of TIVORBEX. A total number of 38 healthy subjects completed the treatments. The food effect on reference drug indomethacin was evaluated from the study IND1-08-01.

Treatments:

Study IND1-12-07.	Study IND1-08-01.
TIVORBEX capsules 40 mg Fasted	Indomethacin IR capsules 50 mg Fasted
TIVORBEX capsules 40 mg Fed	Indomethacin IR capsules 50 mg Fed

There was at least a 7-day washout interval between doses. Blood samples for PK were collected for 32 hours after dosing.

Results:

The Figure 2.4.2a and 2.4.2b shows the plasma concentration-time profiles of TIVORBEX 40 mg and Indomethacin IR capsules 50 mg under fasted and fed conditions. The food effect PK parameters and geometric mean ratios and the 90% CIs for AUC_{0-t} and $AUC_{0-\infty}$and Cmax for indomethacin are presented in Table 2.4.2a and Table 2.4.2b, respectively. The summary of results is shown below:

- 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.

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Figure 2.4.2a: Mean ± SD indomethacin plasma conc.-time profiles for 40 mg TIVORBEX capsules under fasted and fed conditions (Study IND1-12-07)

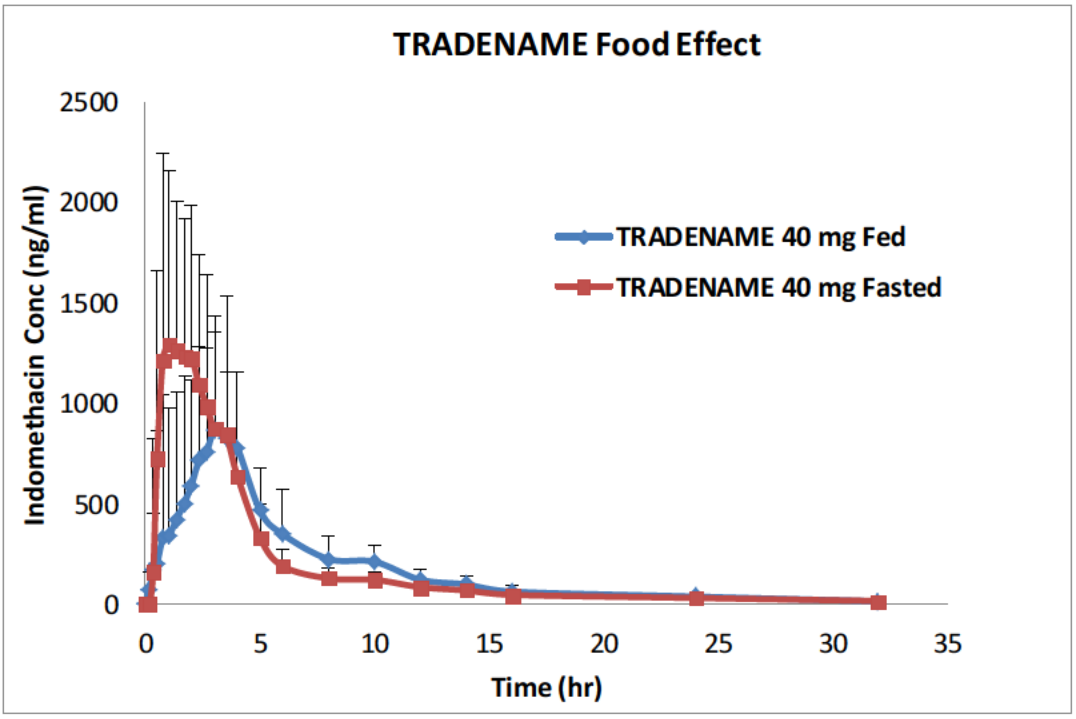

Figure 2.4.2b: Mean ± SD indomethacin plasma conc.-time profiles for indomethacin IR 50 mg capsules (ANDA 070624) under fasted and fed conditions. (Study IND1-08-01).

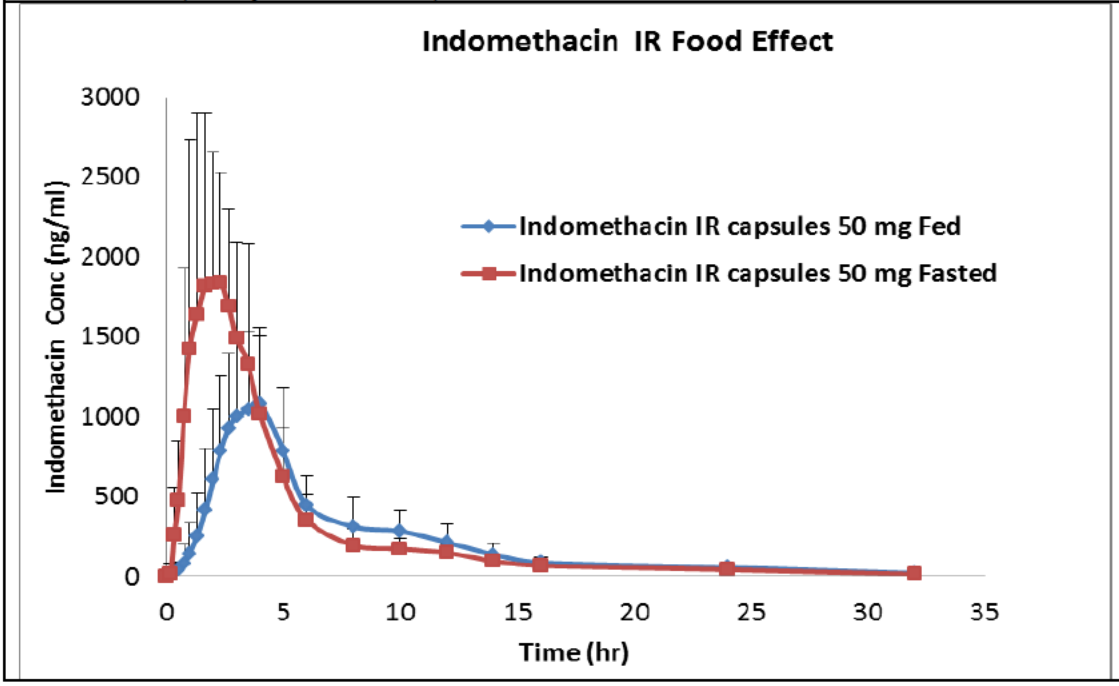

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Table 2.4.2a. Pharmacokinetic parameters of indomethacin after administration of TIVORBEX and indomethacin IR capsules under fasted and fed conditions

Parameter	TIVORBEX Arithmetic mean ± SD (Study IND1-12-07)		Indomethacin IR Capsules Arithmetic mean ± SD (Study IND1-08-01)	
	Fasted	**Fed**	**Fasted**	**Fed**
Cmax (ng/mL)	2368.8 ± 631.4	1395.41 ± 700.12	2759.0 ± 936.3	1407.9 ± 469.5
AUC_{0-t} (hr*ng/mL)	5924.8 ± 1467.1	5463.4 ± 1341.7	8996.7 ± 2130.1	7227.1 ± 605.4
$AUC_{0-\infty}$ (hr*ng/mL)	6110.1 ± 1393.2	5631.8 ± 1366.7	9305.6 ± 2234.4	7530.9 ± 1721.1
Tmax (hr)* (range)	1.67 (0.50 – 3.52)	3.00 (0.57 – 6.00)	2.00 (1.00 - 4.00)	3.50 (1.00 - 8.00)

*median

Table 2.4.2b: Ratio of geometric LS means and 90% CI of AUC and Cmax comparing TIVORBEX and indomethacin IR capsules under fasted and fed conditions.

PK parameter	Treatment Ratio (90% CI of ratio)	
	TIVORBEX Fasted / TIVORBEX Fed	**Indomethacin IR Fasted / Indomethacin IR Fed**
Cmax	0.540 (0.474, 0.615)	0.508 (0.460, 0.562)
AUC_{0-t}	0.910 (0.879, 0.942)	0.806 (0.780, 0.832)
$AUC_{0-\infty}$	0.911 (0.880, 0.944)	0.812 (0.787, 0.838)

Reviewer comments:
The Indocin label does not have the food effect information. The observed food effect in terms of decreased Cmax and delayed for TIVORBEX capsules is comparable to the reference indomethacin capsules and does not warrant labeling recommendations.

2.5. Analytical Section

2.5.1 Are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies? What is the QC sample plan? What are the accuracy, precision and selectivity of the method?

Clinical Facility:
PAREXEL Early Phase Clinical Unit, 3001 Hanover Street, Baltimore, Maryland 21225.

- Clinical study IND1-12-07 study duration was between 05 September 2012 to 20 November 2012

Bio-analytcial Facility:
(b) (4)

- Assay of samples were conducted from 07 November 2012 to 10 December 2012.

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The plasma concentrations of Indomethacin were analyzed using validated LC-MS/MS assays.

Bio-analytical Validation:
The range of calibrators and QCs used for studies were:

- Calibrators: 5.8600, 11.719, 23.443, 46.913, 93.771, 187.54, 375.08, 750.16, 1500.3, 3000.7 and 6001.4 ,ng/mL
- Quality controls: 5.8595, 14.883, 29.403, 58.180, 118.78, 239.99, 479.98, 959.97, 1919.9, and 4799.8 ng/ml

Accuracy and Precision over the range:

- Accuracy (expressed as % bias): -6.1 – 1.6
- Precision (expressed as % CV): 1.9 – 9.4

Retention times:

- Indomethacin ~ 1.58 minutes
- Diclofenac(internal standard) ~ 1.52 minutes
- Total run time: 3 minutes

Recovery (mean extraction yields)

- Indomethacin: ~ 65 % (mean % CV = 7.0)
- Internal standard: ~ 74 % (% CV = 8.9)

Stability:

Stock solution stability:

- Indomethacin: 15 days at RT, at ~5 °C and at ~ -20 °C
- Indomethacin: 15 days at RT, at ~5 °C and at ~ -20 °C

Freeze and thaw stability:

- 3 freeze-thaw cycles

Short-term matrix stability:

- 6 hours at room temperature

Long-term matrix stability:

- 41 days when stored at ~ -20 ºC

On-instrument / post-preparative stability:

- 98.33 hours

3. Detailed Labeling Recommendations

The following labeling comments are proposed by this reviewer. Deletion is shown by Strike-through text and addition is shown by underline text.

Reviewer Comments:

This labeling recommendation for hepatic impairment for TIVORBEX is updated in comparison to previous Indomethacin products. The updated sections are in 2.3 and

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12.3. These recommendations are due to new requirements based on the SEALD LABELING high level comments.

(b) (4)

USE IN SPECIAL POPULATIONS

12.3 Pharmacokinetics

(b) (4)

The relative bioavailability of TIVORBEX 40 mg capsules was compared to indomethacin immediate-release (IR) 50 mg capsules in 38 healthy subjects under fasted in a single-dose crossover study.

TIVORBEX (indomethacin) 40 mg capsules do not result in an equivalent systemic exposure to 50 mg indomethacin IR capsules.

When taken under fasted conditions, a 20% lower dose of indomethacin in TIVORBEX capsules resulted in a 21% lower mean systemic exposure (AUC_{inf}) and an equivalent mean peak concentration (C_{max}) compared to indomethacin IR capsules. The median time to reach peak concentrations (Tmax) was 1.67 hr and 2.02 hr for TIVORBEX capsules and Indomethacin IR capsules, respectively.

There were no differences in elimination half-life between TIVORBEX and indomethacin IR capsules under fasted conditions

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Absorption

Similar to indomethacin IR capsules, following single oral doses of TIVORBEX capsules 20 mg or 40 mg, indomethacin is readily absorbed, attaining peak plasma concentrations of about approximately (b) (4) mcg/mL, respectively, at about 1.67 hours. Indomethacin (b) (4) is virtually 100% bioavailable, with 90% of the dose absorbed within 4 hours following dosing.

Administration of TIVORBEX capsules 20 mg and 40 mg was associated with dose proportional pharmacokinetics.

(b) (4) Taking TIVORBEX with food causes a significant decrease in the rate but not the overall extent of systemic absorption of Indomethacin compared to taking TIVORBEX on an empty stomach. TIVORBEX capsules results in 46% lower C_{max}, 9% lower $AUC_{inf.}$ and 1.33 hr delayed T_{max} (1.67 hr during fasted versus 3.00 hr during fed) under the fed condition compared to the fasted condition.

(b) (4)

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(b) (4)

Distribution
Indomethacin is highly bound to protein in plasma (b) (4) (about 99%) over the expected range of therapeutic plasma concentrations.

(b) (4) Indomethacin crosses the blood-brain barrier and the placenta, and appears in breast milk (b) (4)

Excretion
Indomethacin is (b) (4) eliminated via (b) (4) metabolism (b) (4) Indomethacin undergoes appreciable enterohepatic circulation. About 60% (b) (4) of an oral dose is recovered in urine as drug and metabolites (26 percent as indomethacin and its glucuronide), and 33% is recovered in feces (1.5% as indomethacin). The mean half-life of indomethacin from TIVORBEX Capsules 40 mg is 7.6 hours and is comparable to indomethacin IR capsules 50 mg (7.2 hours).

(b) (4)

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(b) (4)

Reviewer Comments:

- *Sponsor added the statement* (b) (4) *This statement has been delete* (b) (4)

- *Sponsor included* (b) (4) *This sponsor's addition has been deleted and is not there in the Indocin label.* (b) (4)

4.0 Appendices

4.1 Sponsor's Proposed Label

27 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

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4.2 Individual Study Synopses:

Note: Study synopses in this section were extracted from the NDA submission

4.2.1 Study Designs:

IND1-12-07(Phase 1): Relative bioavailability (BA), dose-proportionality and food effect study. This study was conducted with commercial scale formulation and it fulfills the clinical pharmacology information of the proposed product from regulatory requirement perspective.

4.2.2 Study Synopses

Study *IND1-12-07*

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2. SYNOPSIS

Name of Sponsor/Company: Iroko Pharmaceuticals, LLC	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use Only)**
Name of Finished Product: (b) (4) Capsules 20 mg and 40 mg	**Volume:**	
Name of Active Ingredient: Indomethacin	**Page:**	

Title of Study:	A Randomized, Single-Dose, Four-Way Crossover, Relative Bioavailability Study of (b) (4) (indomethacin submicron particle) Capsules 20 mg and 40 mg and Indomethacin Immediate Release 50 mg Capsules in Healthy Subjects	
Principal Investigator:	Olukemi Olugemo, MD	
Study Center(s):	PAREXEL Early Phase Clinical Unit, 3001 South Hanover Street, Baltimore, Maryland 21225, United States of America	
Publication:	None at the time of writing this clinical study report.	
Development Phase:	Phase 1 – Bioavailability, food-effect, dose proportionality	
Studied Period:	**First subject enrolled:**	05 September 2012
	Last subject completed:	20 November 2012

Study Objective(s):

The primary objectives of this study were:

- To determine the relative bioavailability of indomethacin from the 40 mg Test capsules (b) (4) (indomethacin submicron particle) Capsules] versus the 50 mg Reference Indomethacin capsules when administered to healthy subjects under fasting conditions,
- To determine the effect of food on the rate and extent of absorption of a single dose of the 40 mg (Test) formulation (b) (4) Capsules] administered to healthy subjects under fed and fasting conditions,
- To evaluate the dose proportionality between 20 mg and 40 mg Test formulations of (b) (4) Capsules administered to healthy subjects under fasting conditions.

Study Design:

This was a single center, randomized, open label, 4 period, 4 treatment, 4 sequence, single dose crossover PK study in which 40 healthy adult subjects were scheduled to receive 4 separate single dose administrations of study drug. The treatments under investigation were:

Treatment A: (b) (4) Capsules 20 mg (Test) Single Dose: 1 x 20 mg capsule given after a fast on an empty stomach

Treatment B: (b) (4) Capsules 40 mg (Test) Single Dose: 1 x 40 mg capsule given after a fast on an empty stomach

Treatment C: (b) (4) Capsules 40 mg (Test) Single Dose: 1 x 40 mg capsule given 30 minutes after a Standard Food and Drug Administration (FDA) High Fat breakfast

Treatment D: Indomethacin 50 mg capsules (Reference) Single Dose: 1 x 50 mg capsule given after a fast on an empty stomach

Methodology:

Healthy adult male and female subjects who met all study eligibility criteria were randomized equally to 1 of 4 predetermined sequences of treatment administration.

Subjects were administered the investigational medicinal products (IMPs) in the order of their assigned sequence. There was at least a 7-day washout interval between administrations.

The study was divided into a Screening Phase followed by 4 sequential Treatment Periods with intervening Washout Periods scheduled between administrations.

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Name of Sponsor/Company: Iroko Pharmaceuticals, LLC	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
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Study Plan

Assignment	Study Day	Washout Period
Screening Phase	Days -28 to -1	Not applicable
Treatment Period 1	Day 1	Days 2 to 7
Treatment Period 2	Day 8	Days 9 to 14
Treatment Period 3	Day 15	Days 16 to 21
Treatment Period 4	Day 22	End of Treatment

The Screening phase took place within 28 days before the administration of the first dose of IMP. Subjects were required to provide written informed consent to participate in the study before any protocol specified procedures or evaluations were completed. During the Screening phase, subjects were evaluated against the protocol specific inclusion and exclusion criteria to determine their eligibility for participation in the study.

In Treatment Period 1, subjects who met eligibility requirements were admitted to the clinical research unit (CRU) the evening before the scheduled morning dose. All subjects underwent at least a 10-hour overnight fast. The following morning, subjects randomized to receive Treatments A, B, and D were administered a single oral dose of IMP with 240 mL of water on an empty stomach. Subjects randomized to receive Treatment C were administered a single oral dose of IMP with 240 mL of water within 30 minutes after starting the FDA high-fat breakfast.

Subjects were confined to the CRU until at least 32 hours after IMP administration. Blood samples (approximately 4 mL each) for PK analysis were collected at the following times: pre-dose (time 0) and 10, 20, 30, 45 min, 1 hr, 1 hr 20 min, 1 hr 40 min, 2 hr, 2 hr 20 min, 2 hr 40 min, 3 hr, 3 hr 30 min, 4, 5, 6, 8, 10, 12, 14, 16, 24 and 32 hrs after dosing. Blood samples for safety assessments were performed at specified times throughout confinement.

In Treatment Periods 2, 3 and 4, subjects returned to the CRU after at least a 7-day Washout Period (from dose to dose). The same study procedures were performed as in Treatment Period 1; however, the subjects followed the order of their randomly assigned sequences and "crossed over" to a different treatment. A blood sample for safety assessments was collected at the time the last sample was obtained for PK analysis in Treatment Period 4. Subjects who required follow-up for adverse events (AEs), additional physical examinations, or additional vital signs, electrocardiogram (ECG), or clinical laboratory assessments, were to return to the CRU as deemed appropriate by the investigator.

Number of Study Subjects (Planned and Analyzed):

Planned for completion	30
Enrolled and randomized:	41
Completed:	36
Analyzed:	40

Diagnosis and Main Criteria for Inclusion:

The study population consisted of healthy adult males or females between 18 and 55 years of age (inclusive), with a body mass index between 18 and 30 kg/m^2 (inclusive). Subjects were in good health, as determined by lack of clinically significant abnormalities in health and/or laboratory assessments. Acceptable forms of contraception were to be used during the study until at least 7 days after study completion.

Test Product, Treatment A, Dose and Mode of Administration, Batch Number:

Treatment A:	(b) (4) (indomethacin submicron particle) Capsules
Batch number:	L0307815
Mode of administration:	Oral
Strength:	20 mg
Dose:	1 Capsule

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Name of Sponsor/Company: Iroko Pharmaceuticals, LLC	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
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paper (source documents), captured electronically in ClinBase or provided by external vendors.

Summary of Results:

Demographic Characteristics of Subjects:

Forty-one (41) subjects were randomized into treatment and 36 subjects (87.8%) completed all 4 study periods. Five (5) subjects discontinued before study completion, one of whom (Subject 25) was discontinued prior to receiving any study medication. The 40 subjects who received at least one dose of study drug were included in the full analysis set and ranged in age from 19 to 54 years, with a mean age of 36.5 years. There were 33 male subjects (82.5%) and 7 female subjects (17.5%). With regard to race, 24 subjects (60.0%) were Black or African American, 15 subjects (37.5%) were White and 1 subject was American Indian or Alaska Native (2.5%). The mean height was 174.8 cm, with a range of 156 to 188 cm. The mean body weight was 79.41 kg, with a range of 61.8 to 100.4 kg. The mean BMI was 25.97 kg/m^2, with a range of 19.2 to 30.0 kg/m^2. Demographic findings were reflective of a healthy adult population.

Pharmacokinetic Results:

Consistent with the Statistical Analysis Plan, all subjects who received any amount of study drug and had at least 1 non-zero concentration after dosing were included in the pharmacokinetic analyses. A summary of the pharmacokinetic parameters for the 4 treatments is presented in the table below. Statistical test results for the pharmacokinetic parameters for indomethacin are also summarized in the tables that follow.

Pharmacokinetic Parameters of Indomethacin by Treatment (PK Population)

Parameter	Statistics	Treatment A (b) (4) Capsules 20 mg (fast)	Treatment B (b) (4) Capsules 40 mg (fast)	Treatment C (b) (4) Capsules 40 mg (fed)	Treatment D Indomethacin 50 mg capsules (fast)
C_{max} (ng/mL)	n	38	36	38	37
	Mean	1165.85	2368.79	1395.41	2369.40
	SD	367.167	631.376	700.117	969.062
	CV (%)	31.5	26.7	50.2	40.9
	Geometric Mean	1110.05	2284.08	1239.06	2213.90
t_{max} (h)	n	38	36	38	37
	Median	1.670	1.670	3.000	2.020
	Minimum	0.50	0.50	0.57	0.50
	Maximum	5.00	3.52	6.00	5.00
λ_z (1/h)	n	34	33	38	34
	Mean	0.099	0.103	0.110	0.107
	SD	0.0367	0.0350	0.0358	0.0428
	CV (%)	37.3	34.0	32.7	39.9
	Geometric Mean	0.092	0.097	0.104	0.101
$t_{½}$ (h)	n	34	33	38	34
	Mean	8.125	7.622	7.061	7.216
	SD	3.4302	3.2584	2.5167	2.4288
	CV (%)	42.2	42.7	35.6	33.7

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Pharmacokinetic Parameters of Indomethacin by Treatment (PK Population) (continued)

Parameter	Statistics	Treatment A (b) (4) Capsules 20 mg (fast)	Treatment B (b) (4) Capsules 40 mg (fast)	Treatment C (b) (4) Capsules 40 mg (fed)	Treatment D Indomethacin Capsules 50 mg (fast)
AUC_{0-t} (h*ng/mL)	n	38	36	38	37
	Mean	2844.837	5924.813	5463.398	7658.115
	SD	604.3270	1467.0448	1341.6695	1905.6357
	CV (%)	21.2	24.8	24.6	24.9
	Geometric Mean	2786.268	5762.224	5305.443	7440.576
$AUC_{0-\infty}$ (h*ng/mL)	n	34	33	38	34
	Mean	2981.776	6110.064	5631.781	7762.158
	SD	548.7123	1393.1461	1366.6555	1845.5176
	CV (%)	18.4	22.8	24.3	23.8
	Geometric Mean	2934.319	5970.560	5473.893	7563.761

AUC = Area under the curve; C_{max} = Maximum concentration; t_{max} = Time of maximum concentration; $t_{½}$ = half-life

Statistical Analysis of Relative Bioavailability of Indomethacin Plasma Pharmacokinetic Parameters (PK Population) for Treatments B:D (40 mg Test product vs. 50 mg Reference product [fasting conditions])

Parameter (unit)	Treatment	N*	Geometric LS Mean	Geometric LS Mean 95% CI	Treatment Ratio (B/D) (%)	90% CI of Ratio
C_{max} (ng/mL)	B	36	2292.60	(2022.46, 2598.83)	1.034	(0.908, 1.179)
	D	37	2216.38	(1958.21, 2508.58)		
AUC_{0-t} (ng.h/mL)	B	36	5832.63	(5419.25, 6277.54)	0.781	(0.755, 0.809)
	D	37	7466.33	(6938.78, 8033.99)		
$AUC_{0-\infty}$ (ng.h/mL)	B	33	6007.71	(5585.73, 6461.58)	0.786	(0.758, 0.815)
	D	34	7646.23	(7110.44, 8222.40)		

CI = confidence interval; LS: least squares; N = number of subjects in the pharmacokinetic population; % = percentage

Treatment B: (b) (4) Capsules 40 mg (Test) Single Dose: 1 x 40 mg capsule (Fasting)

Treatment D: Indomethacin 50 mg capsules (Reference) Single Dose: 1 x 50 mg capsule (Fasting)

Mixed model ANOVA with fixed effects for treatment, period and sequence, and random effect for subject nested within sequence was utilized.

Least squares (LS) means, Ratio of LS means, and their confidence intervals (CI) were transformed back to the original scale.

* Shows the number of subjects used in the mixed model analysis. This is the number of subjects with non-missing PK parameters.

Under fasting conditions, analysis of the relative bioavailability of indomethacin following administration of (b) (4) Capsules 40 mg and Indomethacin 50 mg capsules indicate that the maximum indomethacin concentrations (C_{max}) of the two drug products were statistically equivalent.

As expected, the overall extent of exposure to indomethacin (AUC_{0-t} and $AUC_{0-\infty}$) following administration of the (b) (4) Capsules 40 mg dose was approximately 22% lower than that observed for the Indomethacin 50 mg

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capsules.

The geometric mean ratio for indomethacin C_{max} of these two treatments was 1.034 and the 90% confidence interval for the geometric mean was well within the 0.8 to 1.25 equivalence limits.

In contrast, the 90% confidence intervals for the geometric mean ratios for AUC_{0-t} and $AUC_{0-\infty}$ were below the 0.8 to 1.25 equivalence limits. Median indomethacin t_{max} values for Tiforbex Capsules 40 mg and Indomethacin 50 mg capsules were 1.67 and 2.02 hours, respectively.

Statistical Analysis of Dose Proportionality for Dose Normalized Indomethacin Plasma Pharmacokinetic Parameters (PK Population) for Treatments B:A (40 mg vs. 20 mg Test Product [Fasted Subjects])

Parameter (unit)	Treatment	N*	Geometric LS Mean	Geometric LS Mean 95% CI	Treatment Ratio (B/A) (%)	90% CI of Ratio
C_{max} (ng/mL)	A	38	55.56	(50.38, 61.27)		
	B	36	57.65	(52.15, 63.74)	1.038	(0.944, 1.140)
AUC_{0-t} (ng.h/mL)	A	38	139.33	(129.44, 149.98)		
	B	36	144.32	(134.00, 155.43)	1.036	(1.003, 1.070)
$AUC_{0-\infty}$ (ng.h/mL)	A	34	146.92	(136.53, 158.09)		
	B	33	149.49	(138.89, 160.91)	1.018	(0.984, 1.052)

CI = confidence interval; LS: least squares; N = number of subjects in the pharmacokinetic population; % = percentage

Treatment A: (b) (4) Capsules 20 mg (Test) Single Dose: 1 x 20 mg capsule (Fasting)

Treatment B: (b) (4) Capsules 40 mg (Test) Single Dose: 1 x 40 mg capsule (Fasting)

Mixed model ANOVA with fixed effects for treatment, period and sequence, and random effect for subject nested within sequence was utilized.

Least squares (LS) means, Ratio of LS means, and their confidence intervals (CI) were transformed back to the original scale. Dependent variable in the analysis was the natural logarithm of the dose normalized PK parameter.

The ANOVA was subset on treatments A and B.

* Shows the number of subjects used in the mixed model analysis. This is the number of subjects with non-missing PK parameters.

Evidence of dose proportionality holds if the estimated ratio of geometric means is close to 1 and if the 90% CI for the ratio of geometric means are within the range 0.8 to 1.25.

For the 20 mg and 40 mg doses of (b) (4) Capsules under fasting conditions, dose proportional increases in indomethacin AUC_{0-t} and $AUC_{0-\infty}$ were confirmed by comparison of dose-normalized ln-transformed AUC_{0-t} and $AUC_{0-\infty}$. The 90% CI of the ratios of the dose-normalized geometric means of indomethacin AUC_{0-t} and $AUC_{0-\infty}$ were within the range 0.8 to 1.25, and the dose-normalized geometric mean ratios of indomethacin AUC_{0-t} and $AUC_{0-\infty}$ of (b) (4) Capsules 20 mg and 40 mg were 1.036 and 1.018, respectively, close to the value of 1.00. The 90% CI of the ratio of the dose-normalized geometric means of indomethacin C_{max} of (b) (4) Capsules 20 mg and 40 mg was also within the 0.8 to 1.25 range; the dose-normalized geometric mean ratio of indomethacin C_{max} between the doses of (b) (4) Capsules 20 and 40 mg was 1.038.

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Statistical Analysis of Food-Effect for Indomethacin Plasma Pharmacokinetic Parameters (PK Population) (continued)

Parameter (unit)	Treatment	N*	Geometric LS Mean	Geometric LS Mean 95% CI
Parameter (unit)	**Treatment Comparison**	**N***	**Hodges-Lehmann Estimate Median Difference**	**90% CI for Estimate of Median Difference**
t_{max} (h)	C vs. B	36	1.36	(1.00, 2.00)

CI = confidence interval; LS: least squares; N = number of subjects in the pharmacokinetic population; % = percentage

Treatment B: (b) (4) Capsules 40 mg (Test) Single Dose: 1 x 40 mg capsule (Fasting)
Treatment C: (b) (4) Capsules 40 mg (Test) Single Dose: 1 x 40 mg capsule (Fed)
Mixed model ANOVA with fixed effects for treatment, period and sequence, and random effect for subject nested within sequence was utilized.
Least squares (LS) means, Ratio of LS means, and their confidence intervals (CI) were transformed back to the original scale. Dependent variable in the analysis was the natural logarithm of the PK parameter. In all comparisons the fasting treatment was used as the reference treatment. * Shows the number of subjects used in the mixed model analysis. This is the number of subjects with non-missing PK parameters. In addition for t_{max}: The difference in medians and its 90% confidence interval was estimated using the methodology of Hodges-Lehmann for paired samples. In addition for t_{max}: The CI of the median difference was obtained by applying a normal approximation to the Wilcoxon Signed-Rank distribution. In addition for t_{max}: 'N' is the number of subjects used in the analysis. This is the number of subjects with complete data for both treatments.

There was evidence of a food effect for (b) (4) Capsules 40 mg with respect to the rate of absorption. The geometric mean ratio for indomethacin C_{max} was 0.540 indicating that food decreased the rate of absorption by approximately 50%. The 90% confidence interval for C_{max} was well below the lower limit of the interval 0.8 to 1.25.
In contrast, there was no effect of food on the overall extent of absorption. The geometric mean ratios for indomethacin AUC_{0-t} and $AUC_{0-\infty}$ were 0.910 and 0.911, respectively. The 90% confidence intervals for the geometric mean ratios of indomethacin AUC_{0-t} and $AUC_{0-\infty}$ for (b) (4) Capsules 40 mg administered under fed versus fasting conditions were within the interval 0.8 to 1.25.
Median indomethacin t_{max} was 1.67 hours when (b) (4) Capsules 40 mg were administered under fasted conditions compared to 3.00 hours when administered under fed conditions. The difference (90% CI) in median tmax values was 1.36 (1.00, 2.00) hours for the comparison of indomethacin tmax under fed and fasted conditions. These results indicate a definite food effect on the rate (C_{max} and t_{max}) but not the overall extent (AUC_{0-t} and $AUC_{0-\infty}$) of indomethacin absorption for (b) (4) Capsules 40 mg.

Safety Results:
Ten (10) subjects (25.0%) reported 14 AEs during the study. Nine (9) subjects (22.50%) reported 12 AEs during or following receipt of IMP. Eight (8) TEAEs were reported by 6 subjects (16.07%) during or following receipt of (b) (4) Capsules (Test Product) and 4 TEAEs were reported by 3 subjects (8.11%) during or following receipt of Indomethacin capsules (Reference Product). The other 2 AEs were reported by 2 subjects and occurred prior to first dosing. None of the reported AEs were considered to be related to study drug administration. No subject discontinued before study completion due to an AE and there were no deaths or SAEs.
No clinically significant abnormalities were observed in clinical laboratory parameters after assessment by the Investigator. Review by the Investigator of vital signs, ECGs and physical examinations did not reveal any clinically significant abnormalities.

Reference ID: 3437613

Name of Sponsor/Company: Iroko Pharmaceuticals, LLC	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product: (b) (4) Capsules 20 mg and 40 mg	Volume:	
Name of Active Ingredient: Indomethacin	Page:	

Statistical Analysis of Food-Effect for Indomethacin Plasma Pharmacokinetic Parameters (PK Population) (continued)

Parameter (unit)	Treatment	N*	Geometric LS Mean	Geometric LS Mean 95% CI
Parameter (unit)	**Treatment Comparison**	**N***	**Hodges-Lehmann Estimate Median Difference**	**90% CI for Estimate of Median Difference**
t_{max} (h)	C vs. B	36	1.36	(1.00, 2.00)

CI = confidence interval; LS: least squares; N = number of subjects in the pharmacokinetic population; % = percentage

Treatment B: (b) (4) Capsules 40 mg (Test) Single Dose: 1 x 40 mg capsule (Fasting)
Treatment C: (b) (4) Capsules 40 mg (Test) Single Dose: 1 x 40 mg capsule (Fed)
Mixed model ANOVA with fixed effects for treatment, period and sequence, and random effect for subject nested within sequence was utilized.
Least squares (LS) means, Ratio of LS means, and their confidence intervals (CI) were transformed back to the original scale. Dependent variable in the analysis was the natural logarithm of the PK parameter. In all comparisons the fasting treatment was used as the reference treatment. * Shows the number of subjects used in the mixed model analysis. This is the number of subjects with non-missing PK parameters. In addition for t_{max}: The difference in medians and its 90% confidence interval was estimated using the methodology of Hodges-Lehmann for paired samples. In addition for t_{max}: The CI of the median difference was obtained by applying a normal approximation to the Wilcoxon Signed-Rank distribution. In addition for t_{max}: 'N' is the number of subjects used in the analysis. This is the number of subjects with complete data for both treatments.

There was evidence of a food effect for (b) (4) Capsules 40 mg with respect to the rate of absorption. The geometric mean ratio for indomethacin C_{max} was 0.540 indicating that food decreased the rate of absorption by approximately 50%. The 90% confidence interval for C_{max} was well below the lower limit of the interval 0.8 to 1.25.
In contrast, there was no effect of food on the overall extent of absorption. The geometric mean ratios for indomethacin AUC_{0-t} and $AUC_{0-\infty}$ were 0.910 and 0.911, respectively. The 90% confidence intervals for the geometric mean ratios of indomethacin AUC_{0-t} and $AUC_{0-\infty}$ for (b) (4) Capsules 40 mg administered under fed versus fasting conditions were within the interval 0.8 to 1.25.
Median indomethacin t_{max} was 1.67 hours when (b) (4) Capsules 40 mg were administered under fasted conditions compared to 3.00 hours when administered under fed conditions. The difference (90% CI) in median tmax values was 1.36 (1.00, 2.00) hours for the comparison of indomethacin tmax under fed and fasted conditions. These results indicate a definite food effect on the rate (C_{max} and t_{max}) but not the overall extent (AUC_{0-t} and $AUC_{0-\infty}$) of indomethacin absorption for (b) (4) Capsules 40 mg.

Safety Results:
Ten (10) subjects (25.0%) reported 14 AEs during the study. Nine (9) subjects (22.50%) reported 12 AEs during or following receipt of IMP. Eight (8) TEAEs were reported by 6 subjects (16.07%) during or following receipt of (b) (4) Capsules (Test Product) and 4 TEAEs were reported by 3 subjects (8.11%) during or following receipt of Indomethacin capsules (Reference Product). The other 2 AEs were reported by 2 subjects and occurred prior to first dosing. None of the reported AEs were considered to be related to study drug administration. No subject discontinued before study completion due to an AE and there were no deaths or SAEs.
No clinically significant abnormalities were observed in clinical laboratory parameters after assessment by the Investigator. Review by the Investigator of vital signs, ECGs and physical examinations did not reveal any clinically significant abnormalities.

Reference ID: 3437613

Name of Sponsor/Company: Iroko Pharmaceuticals, LLC	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product: (b) (4) Capsules 20 mg and 40 mg	Volume:	
Name of Active Ingredient: Indomethacin	Page:	

Conclusion:

An earlier Phase 1 (IND1-08-01) study evaluated the PK parameters using the Proof of Concept (POC) Formulation for (b) (4) Capsules 20 mg and 40 mg. Although there was no evidence of differences in the in vitro performance characteristics of (b) (4) Capsules before and following modifications to the manufacturing process, the current study (IND1-12-07) was conducted to characterize the in vivo absorption kinetics of the planned Commercial Formulation of (b) (4) Capsules 20 mg and 40 mg.

Results from this study showed that the overall systemic exposure to indomethacin from the Test Product, (b) (4) Capsules 40 mg, was approximately 22% lower (compared to the overall systemic exposure from the Reference product, Indomethacin 50 mg capsules), and supported the development rationale. In addition, the maximum indomethacin concentrations (C_{max}) following dosing with (b) (4) Capsules 40 mg and Indomethacin 50 mg were statistically equivalent.

Consistent with other NSAIDs, food decreased the rate (C_{max}) but not the extent of indomethacin absorption (AUC_{0-t} and $AUC_{0-\infty}$) of (b) (4) Capsules 40 mg when administered under fed conditions.

The overall analysis of (b) (4) Capsules 20 mg and 40 mg showed dose proportionality based on the assessment of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$.

(b) (4) Capsules and Indomethacin capsules were generally well tolerated and none of the reported AEs were considered to be related to study drug administration. There were no withdrawals due to AEs and no deaths or SAEs occurred.

In summary, the pharmacokinetics of (b) (4) Capsules manufactured using an optimized process have been fully characterized and are consistent with the results for the POC Formulation in the previous Phase 1 (IND1-08-01) study. The maximum indomethacin concentrations (C_{max}) following dosing with (b) (4) Capsules 40 mg and Indomethacin 50 mg capsules were statistically equivalent; as expected, the overall indomethacin systemic exposure following administration of (b) (4) Capsules 40 mg was proportionate to the indomethacin dose, approximately 20% lower than indomethacin systemic exposure compared with the Indomethacin 50 mg capsules.

Date of Report: Final 1.0, 14 February 2013

This study was conducted in compliance with International Conference on Harmonization (ICH) Good Clinical Practice guidelines (GCP) and the Declaration of Helsinki.

Reference ID: 3437613

4.3 Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	***NDA*-204768**	**Brand Name**	*TIVORBEX*
OCP Division (I, II, III, IV, V)	***II***	**Generic Name**	***Indomethacin***
Medical Division	***DAAAP***	**Drug Class**	***NSAID***
OCP Reviewer	***Suresh B Naraharisetti***	**Indication(s)**	***Acute pain***
OCP Team Leader	***Yun Xu***	**Dosage Form**	***Immediate- release Capsule***
Pharmacometrics Reviewer		**Dosing Regimen**	***BID or TID***
Date of Submission		**Route of Administration**	***Oral***
Estimated Due Date of OCP Review		**Sponsor**	**Iroko Pharma**
Medical Division Due Date		**Priority Classification**	
PDUFA Due Date	**February 28, 2014**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods	**X**	**1**		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -		**1**		
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				

Reference ID: 3437613

In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	**X**	**1**		Indocin as reference Mylan ANDA 070624 in R BA study
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	**X**	**1**		
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				**Yes**
Literature References				
Total Number of Studies		**4**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			

Reference ID: 3437613

7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

BACKGROUND

Reference ID: 3437613

Iroko Pharmaceuticals submitted a 505 (b) (2) NDA (204768) for TIVORBEX for the indication of treatment of mild to moderate acute pain in adults. As a 505(b) (2) NDA: Sponsor is relying on the Agency's findings on the safety and efficacy of Indocin (25 and 50 mg, NDA 016059, discontinued for reasons not related to safety or efficacy). For establishing the clinical bridge, Iroko has conducted a relative bioavailability (BA) against Indomethacin 50 mg capsules (Mylan Pharmaceuticals, Inc., ANDA 070624).

In support of this NDA, sponsor conducted the following Clinical Pharmacology/Clinical studies:

Clinical Pharmacology Studies:

- **Phase 1 IND1-08-01:** Relative BA, food effect and dose-proportionality study (with proof-of concept formulation).
  - Design: Single-dose, five-way crossover, relative bioavailability study of indomethacin 20 mg, 40 mg (test),versus 50 mg capsules (reference) in healthy subjects under fasted and fed conditions.
  - This study was conducted with proof-of concept formulation. The study was repeated with similar design using commercial scale formulation in the IND1-12-07. The PK information of Mylan Indomethacin from this study will be reviewed.
- **Phase 1 IND1-12-07:** Relative BA, food effect and dose proportionality study (pivotal study with commercial formulation)
  - Design: A randomized, single-dose, four-way crossover, relative bioavailability study of TIVORBEX (indomethacin submicron particle) capsules 20 mg and 40 mg and indomethacin immediate release 50 mg capsules in healthy subjects (n=35).
  - This study was conducted with commercial scale formulation. The study is pivotal study assessing relative bioavailability, dose proportionality and food effect of TIVORBEX capsules.

Clinical Studies:

- **Phase 2 IND2-08-03** (with proof-of concept formulation):
  - Design: A phase 2, randomized, double-blind, single-dose, parallel-group, active- and placebo-controlled study of TIVORBEX capsules for the treatment of pain after surgical removal of impacted third molars (n=203)
  - This study was conducted with proof-of concept formulation.
- **Phase 3 IND3-08-04b-** Pivotal trail (with commercial formulation):
  - Design: A phase 3, randomized, double-blind, multiple-dose, parallel-group, active- and placebo-controlled study of TIVORBEXcapsules for the treatment of acute postoperative pain after bunionectomy (n= 462)
  - This study was conducted with a commercial scale formulation
  - The trial evaluated the safety and efficacy of 3 dosing regimens of TIVORBEX Capsules (40 mg 3 times daily [TID], 40 mg twice daily [BID], or 20 mg TID) in subjects with acute postoperative pain after bunionectomy. The duration of treatment is 48 hours.
- **Phase 3 IND3-10-06** (with commercial formulation)**:**
  - Design: A phase 3, randomized, double-blind, multiple-dose, parallel-group, placebo-controlled study of TIVORBEXcapsules for the treatment of acute postoperative pain after bunionectomy (n=373)
  - This study was conducted with a commercial scale formulation

Reference ID: 3437613

- The trial evaluated the safety and efficacy of 3 dosing regimens of TIVORBEX Capsules (40 mg TID, 40 mg BID, or 20 mg TID). The duration of treatment is 48 hours.

Suresh Babu Naraharisetti	June 18, 2013
Reviewing Clinical Pharmacologist	Date
Xu Yun	June 18, 2013
Team Leader/Supervisor	Date

Reference ID: 3437613

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

/s/

SURESH B NARAHARISETTI
01/16/2014

YUN XU
01/16/2014

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	***NDA*-204768**	**Brand Name**	(b) (4)
OCP Division (I, II, III, IV, V)	***II***	**Generic Name**	***Indomethacin***
Medical Division	***DAAAP***	**Drug Class**	***NSAID***
OCP Reviewer	***Suresh B Naraharisetti***	**Indication(s)**	***Acute pain***
OCP Team Leader	***Yun Xu***	**Dosage Form**	***Immediate- release Capsule***
Pharmacometrics Reviewer		**Dosing Regimen**	***BID or TID***
Date of Submission		**Route of Administration**	***Oral***
Estimated Due Date of OCP Review		**Sponsor**	**Iroko Pharma**
Medical Division Due Date		**Priority Classification**	
PDUFA Due Date	**February 28, 2014**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods	**X**	**1**		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -		**1**		
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	**X**	**1**		Indocin as reference Mylan ANDA 070624 in R BA study
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	**X**	**1**		
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				**Yes**
Literature References				
Total Number of Studies		**4**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
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File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

BACKGROUND

Iroko Pharmaceuticals submitted a 505 (b) (2) NDA (204768) for [redacted] (b) (4) the indication of treatment of mild to moderate acute pain in adults. As a 505(b) (2) NDA: Sponsor is relying on the Agency's findings on the safety and efficacy of Indocin (25 and 50 mg, NDA 016059, discontinued for reasons not related to safety or efficacy). For establishing the clinical bridge, Iroko has conducted a relative bioavailability (BA) against Indomethacin 50 mg capsules (Mylan Pharmaceuticals, Inc., ANDA 070624).

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

In support of this NDA, sponsor conducted the following Clinical Pharmacology/Clinical studies:

Clinical Pharmacology Studies:

- **Phase 1 IND1-08-01:** Relative BA, food effect and dose-proportionality study (with proof-of concept formulation).
  - Design: Single-dose, five-way crossover, relative bioavailability study of indomethacin 20 mg, 40 mg (test),versus 50 mg capsules (reference) in healthy subjects under fasted and fed conditions.
  - This study was conducted with proof-of concept formulation. The study was repeated with similar design using commercial scale formulation in the IND1-12-07. The PK information of Mylan Indomethacin from this study will be reviewed.

- **Phase 1 IND1-12-07:** Relative BA, food effect and dose proportionality study (pivotal study with commercial formulation)
  - Design: A randomized, single-dose, four-way crossover, relative bioavailability study of (b) (4) (indomethacin submicron particle) capsules 20 mg and 40 mg and indomethacin immediate release 50 mg capsules in healthy subjects (n=35).
  - This study was conducted with commercial scale formulation. The study is pivotal study assessing relative bioavailability, dose proportionality and food effect of (b) (4) capsules.

Clinical Studies:

- **Phase 2 IND2-08-03** (with proof-of concept formulation):
  - Design: A phase 2, randomized, double-blind, single-dose, parallel-group, active- and placebo-controlled study of (b) (4) capsules for the treatment of pain after surgical removal of impacted third molars (n=203)
  - This study was conducted with proof-of concept formulation.

- **Phase 3 IND3-08-04b-** Pivotal trail (with commercial formulation):
  - Design: A phase 3, randomized, double-blind, multiple-dose, parallel-group, active- and placebo-controlled study of (b) (4) capsules for the treatment of acute postoperative pain after bunionectomy (n= 462)
  - This study was conducted with a commercial scale formulation
  - The trial evaluated the safety and efficacy of 3 dosing regimens of (b) (4) Capsules (40 mg 3 times daily [TID], 40 mg twice daily [BID], or 20 mg TID) in subjects with acute postoperative pain after bunionectomy. The duration of treatment is 48 hours.

- **Phase 3 IND3-10-06** (with commercial formulation)**:**
  - Design: A phase 3, randomized, double-blind, multiple-dose, parallel-group, placebo-controlled study of (b) (4) capsules for the treatment of acute postoperative pain after bunionectomy (n=373)
  - This study was conducted with a commercial scale formulation
  - The trial evaluated the safety and efficacy of 3 dosing regimens of (b) (4) Capsules (40 mg TID, 40 mg BID, or 20 mg TID). The duration of treatment is 48 hours.

The clinical pharmacology review will focus on the, Study Phase 1 IND1-12-07 that used final to-be-marketed formulation, and the Study IND1-08-01 for the food effect of the reference product.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Suresh Babu Naraharisetti	June 18, 2013
Reviewing Clinical Pharmacologist	Date
Xu Yun	June 18, 2013
Team Leader/Supervisor	Date

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

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

/s/

SURESH B NARAHARISETTI
06/20/2013

YUN XU
06/20/2013