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APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	204-768
Supporting document/s:	000/Original submission
CDER stamp date:	4/30/2013
Product:	Tivorbex® (Indomethacin)
Indication:	Treatment of mild to moderate acute pain
Applicant:	Iroko Pharmaceuticals, LLC, Philadelphia, PA
Review Division:	Division of Anesthesia, Analgesia, and Addiction Products (HFD-170)
Reviewer:	Z. Alex Xu, PhD, DABT
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TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

Indomethacin is a nonsteroidal anti-inflammatory drug (NSAID). It was first approved by the Agency in 1965 as Indocin® 25 mg and 50 mg capsules (Merck and Co. Inc., NDA 016-059) for treatment of Moderate to severe rheumatoid arthritis, ankylosing spondylitis, and osteoarthritis. In addition, Indocin was also indicated for acute painful shoulder (bursitis and/or tendinitis) and gouty arthritis. Indocin was discontinued for reasons not related to safety or efficacy. Various formulations of indomethacin were approved thereafter. This submission is a 505(b)(2) application referencing the Agency's prior findings of safety and efficacy of Indocin oral capsule (NDA 016-059), along with results of clinical trials conducted by the Applicant, seeking approval of Tivorbex (indomethacin submicron particle) for treatment of mild to moderate acute pain in adults.

Since Indocin capsules are no longer available because of the discontinuation in the market, generic Indomethacin 50 mg capsules manufactured by Mylan pharmaceutical (ANDA 070624) were chosen as an appropriate comparator for Tivorbex capsules in the clinical trials based on its listing as an approved drug with therapeutic equivalence. There is limited nonclinical information submitted to support the approval of Tivorbex. Tivorbex is a reformulation of indomethacin with reduced particle size (submicron particle) which was hypothesized to improve the bioavailability after oral administration. Of note, reduction of particle size does not appear to impose additional risk of toxicity since the particles will be dissolved in gastric fluid after administration. The Applicant proposed that a 20% reduction in the indomethacin dose of Tivorbex could provide comparable systemic exposure to the Indomethacin 50 mg tablets, thus, offer the potential to improve the safety profile of this NSAID compound. However, clinical studies did not prove this hypothesis. The recommended maximum dosage is 40 mg TID which is covered by the recommended maximum dosage in Indocin label (50 mg TID) which therefore is expected to be within the systemic exposure associated with approved use. In addition, the treatment duration for Tivorbex is not longer than that of Indocin as suggested by the indication. Therefore, nonclinical toxicity studies are not needed for Tivorbex NDA submission. The excipients in the drug formulation are not novel [redacted (b) (4)] The manufacture of drug substance was according to DMF [redacted (b) (4)] file which was also used for the drug substances of other FDA-approved indomethacin drug products. All impurities in the drug substance are below the qualification level as required by the ICH Q3A and Q3B guidance. Computational toxicity analysis which is also known as quantitative structure-relationship analysis (QSAR) was conducted by the Applicant to investigate the potential for genotoxicity, which is consistent with the Agency's current thinking. The Applicant also provided justification of residual solvent levels in the drug substance according to ICH Q3C.

1.2 Brief Discussion of Nonclinical Findings

Five known impurities were identified in the drug substances and drug product (b) (4) [redacted] According to the specifications of the drug substance, the level of these known impurities is no more than (NMT) (b) (4) of the drug substance, which is lower than the qualification threshold level as required by ICH guidance *Q3A: impurities in new drug substances*. In addition, the levels of these impurities in the drug product are NMT (b) (4) in the 20 mg and 40 mg strength capsule, respectively, according to the release and shelf-life specifications of the drug product. These specifications are below the qualification threshold levels required by the ICH guidance *Q3B: impurities in new drug products*, when the daily intake of drug product is 10 -100 mg and 100 mg - 2 g, respectively. Therefore, additional toxicity studies for impurity qualification as required by ICH Q3 guidance are not needed for the Tivorbex NDA. For impurities that are less than qualification threshold but with a structural alert for genotoxicity, a computational genotoxicity assessment is required for qualification. While the CMC review identified structural alert groups for genotoxicity in (b) (4) [redacted] impurities, the Applicant conducted a computational toxicity evaluation to assess the potential genotoxicity of the 5 impurities using MC4PC system. MC4PC is a knowledge-based system designed to evaluate/predict the associations between the structure of the chemicals and their potential activities in a specific biological assay such as Ames assay, in vitro chromosomal assay, and in vivo micronucleus assay, etc. MC4PC performs analysis using expert modules developed by the Computational toxicity group (CTG) group of the US FDA in collaboration with MultiCASE Inc. The results of the analysis conducted by the Applicant predicted that all 5 impurities would be negative in Ames assay, *in vitro* gene mutation assay, *in vitro* chromosomal assay, *in vivo* micronucleus assay, and *in vivo* gene mutation assay, suggesting these are expected to be non-genotoxic.

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) [redacted] would be positive in Ames assay.

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.

The Applicant also provided justification for the specification limit of (b) (4) a residual solvent that is not included in ICH Q3C, in the drug substance. This justification report used methods for establishing exposure limits as recommended in ICH Q3C to demonstrate that a daily dose (b) (4) is not likely to produce significant toxic effects in human based on available nonclinical information in the public domain. This evaluation appears to be appropriate. Similarly, since indomethacin drug substance with same (b) (4) specification limit has been used in FDA-approved drug products, the level (b) (4) in the drug substance is considered to be acceptable. This justification is not needed for approval of Tivorbex.

A pharmacokinetic study was included in this submission to compare the bioavailability between the indomethacin submicron formulation and Mylan Indomethacin oral capsule in beagle dogs. In this study, 3 groups (6 dogs/group) were administered Mylan 25 mg capsule, indomethacin submicron capsule 25 mg or 20 mg capsule. The 20-mg indomethacin submicron particle formulation appeared to be similar in dose-normalized C_{max} and AUC as compared to the Mylan 25 mg capsule. However, the 25-mg indomethacin submicron particle formulation was significantly lower in dose-normalized C_{max} and AUC as compared to the Mylan 25 mg capsule (↓~ 40%). The T_{max} was 1.67, 1.21, and 0.71 hours for Mylan indomethacin 25 mg capsule, indomethacin submicron 25 mg capsule, and indomethacin submicron 20 mg capsule, respectively, suggesting the reduction in indomethacin particles may be associated with a faster absorption. This study is not required for NDA approval since human PK data of Tivorbex are available.

In addition, the Applicant conducted nonclinical literature search using National Library of Medicine (NLM, PUBMED) as the search engine with publication period from 1978 – 2012, attempting to support the efficacy and safety of indomethacin. Since the safety of Tivorbex is covered in dosage and duration by the referenced FDA-approved drug product, Indocin, these publications are not needed to support the safety of Tivorbex. In

addition, no fundamentally new information is contained in these publications that is relevant for the Tivorbex label; therefore, publications were not formally evaluated.

In summary, the Tivorbex NDA references Indocin oral capsule to support the safety of dosage and duration; therefore, nonclinical toxicity studies are not needed. There are no safety issues for the excipients. The specification limits of the drug substance are the same to the indomethacin drug substance that are used in some FDA-approved drug products, thus, considered to be acceptable.

1.3 Recommendations

1.3.1 Approvability

Tivorbex may be approved for the proposed indication from nonclinical perspective

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

There is no new nonclinical information added in the label of Tivorbex as compared to most recently approved Indocin label. However, the nonclinical sections were re-written for the Tivorbex label to convert the Pregnancy (8.1), (b) (4) and Nursing mother (8.3) section into PLLR format. In addition, human dose multiples of the doses used in animal studies are included in Tivorbex label.

The following is the proposed label sections containing nonclinical information. Of note, section 8.1 and 8.3 were completed by nonclinical review group and Pediatric and Maternal Health Staff (PMHS). (b) (4)

8.1 Pregnancy

Pregnancy Category C prior to 30 weeks gestation; Category D starting at 30 weeks gestation.

Risk Summary
There are no adequate and well-controlled studies of TIVORBEX in pregnant women. Starting at 30 weeks gestation, **Error! Reference source not found.**, and other NSAIDs, should be avoided by pregnant women as premature closure of the ductus arteriosus in the fetus may occur. TIVORBEX can cause fetal harm when administered starting at 30 weeks gestation. If the drug is used during this time period in pregnancy, the patient should be apprised of the potential hazard to the fetus. Prior to 30 weeks gestation, TIVORBEX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In animal reproduction studies, retarded fetal ossification was observed with administration of indomethacin to mice and rats during organogenesis at doses 0.16 and 0.32 times, respectively, the maximum recommended dose (MRHD).

Clinical Considerations
Fetal and Neonatal Adverse Reactions
The known effects of indomethacin and other NSAIDS on the human fetus during the third trimester of pregnancy include: constriction of the ductus arteriosus, tricuspid incompetence, and pulmonary hypertension; non-closure of the ductus arteriosus postnatally which may be resistant

to medical management; myocardial degenerative changes, platelet dysfunction with resultant bleeding, intracranial bleeding, renal dysfunction or failure, renal injury/dysgenesis which may result in prolonged or permanent renal failure, oligohydramnios, gastrointestinal bleeding or perforation, and increased risk of necrotizing enterocolitis.

Labor or Delivery
The effects of TIVORBEX on labor and delivery in pregnant women are unknown. In rat studies, maternal exposure to NSAIDs, as with other drugs known to inhibit prostaglandin synthesis, increased the incidence of dystocia, delayed parturition, and decreased pup survival.

Data

Animal data

Reproductive studies were conducted in mice and rats at dosages of 0.5, 1.0, 2.0, and 4.0 mg/kg/day. Except for retarded fetal ossification at 4 mg/kg/day (0.16 times [mice] and 0.32 times [rats] the maximum recommended human dose [MRHD] on a mg/m^2 basis, respectively) considered secondary to the decreased average fetal weights, no increase in fetal malformations was observed as compared with control groups. Other studies in mice reported in the literature using higher doses (5 to 15 mg/kg/day, 0.20 to 0.60 times MRHD on a mg/m^2 basis) have described maternal toxicity and death, increased fetal resorptions, and fetal malformations. Comparable studies in rodents using high doses of aspirin have shown similar maternal and fetal effects.

Maternal indomethacin administration of 4.0 mg/kg/day during the last 3 days of gestation was associated with an increased incidence of neuronal necrosis in the diencephalon in the live-born fetuses however no increase in neuronal necrosis was observed at 2.0 mg/kg/day as compared to the control groups. Administration of 0.5 or 4.0 mg/kg/day to offspring during the first 3 days of life did not cause an increase in neuronal necrosis at either dose level.

8.3 Nursing Mothers

Based on available published data, indomethacin may be present in human milk. In one study, levels of indomethacin in breast milk were below the sensitivity of the assay (<20 mcg/L) in 11 of 15 women using doses ranging from 75 mg orally to 300 mg rectally daily (0.94 to 4.29 mg/kg daily) in the postpartum period. Based on these levels, the average dose present in breast milk was estimated to be 0.27% of the maternal weight-adjusted dose. In another study indomethacin levels were measured in the (b) (4) breast milk of 8 postpartum women using doses of 75 mg daily and the results were used to calculate an infant daily dose. The estimated infant dose of indomethacin (b) (4) breast milk was less than 30 µg/day or 4.5 µg/ kg/day assuming breast milk intake of 150 ml/kg/day. This is 0.5% of the maternal weight-adjusted dosage or about 3% of the neonatal dose for treatment of patent ductus arteriosus. The developmental and health benefits of human milk feeding should be considered along with the mother's clinical need for TIVORBEX and any potential adverse effects on the human milk-fed child from the drug or from the underlying maternal condition. Exercise caution when TIVORBEX is administered to a nursing woman.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis: In an 81-week chronic oral toxicity study in the rat at doses up to 1 mg/kg/day (0.08 times the MRHD on a mg/m^2 basis), indomethacin had no tumorigenic effect. Indomethacin produced no neoplastic or hyperplastic changes related to treatment in carcinogenic studies in the rat (dosing period 73 to 110 weeks) and the mouse (dosing period 62 to 88 weeks) at doses

up to 1.5 mg/kg/day (0.06 times [mice] and 0.12 times [rats] the MRHD on a mg/m^2 basis, respectively).

Mutagenesis: Indomethacin did not have any mutagenic effect in in vitro bacterial tests (b) (4) and a series of in vivo tests including the host-mediated assay, sex-linked recessive lethals in Drosophila, and the micronucleus test in mice.

Impairment of Fertility: Indomethacin at dosage levels up to 0.5 mg/kg/day had no effect on fertility in mice in a two generation reproduction study (0.02 times the MRHD on a mg/m^2 basis) or a two litter reproduction study in rats (0.04 times the MRHD on a mg/m^2 basis).

2 Drug Information

2.1 Drug

CAS Registry Number (Optional)

Generic Name Indomethacin

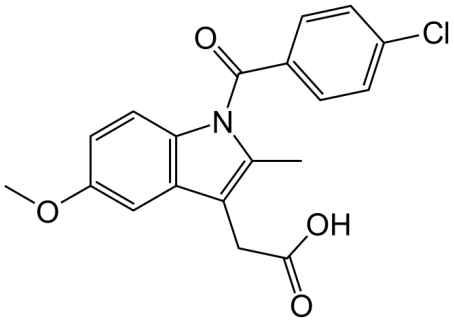
Code Name Indomethacin

Chemical Name: 1-(ρ-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid

Molecular Formula/Molecular Weight

$C_{19}H_{16}ClNO_4$; MW = 357.8

Structure or Biochemical Description



Pharmacologic Class: Nonsteroidal Anti-inflammatory Drug

2.2 Relevant INDs, NDAs, BLAs and DMFs

Tivorbex was developed under IND 101,940. The drug substance referenced DMF (b) (4) Approved indomethacin drug products are shown in the table below.

List of Approved indomethacin drug products

NDA No.	Drug name	Active ingredient	Date of approval	Formulation	Indication	Marketing status
16-059	Indocin	indomethacin	1965	Oral capsule	Treatment of Moderate to severe RA, ankylosing spondylitis, and OA. Treatment for acute painful shoulder and gouty arthritis	discontinued
17-814	Indocin	indomethacin	1984	Suppository, rectal		discontinued
18-332	Indocin	indomethacin	1985	Oral suspension		prescription
18-878	Indocin	indomethacin	1985	Injectable, IV injection	Close a hemodynamically significant patent ductus arteriosus in premature infants weighing	prescription
22-536	Indomethacin	indomethacin	2010	Injectable, IV injection		prescription
In addition, oral capsules with various strengths of indomethacin were approved under NDA 18-690, 18-730, 18-806, 18-829, 18-851, 18-858.						

2.3 Drug Formulation

The composition of the drug product is shown below as extracted from the submission

Table 3.2.P.1.2-1 Composition of (b) (4) Capsules 20 mg

Component	Amount per capsule (mg/capsule weight)	Function	Quality Standard
Indomethacin, USP	20.00	Active pharmaceutical ingredient	(b) (4)
Lactose monohydrate	(b) (4)		
Microcrystalline cellulose			
Croscarmellose sodium			
Sodium lauryl sulfate			
Sodium stearyl fumarate			
Total capsule fill weight			
(b) (4) capsule consisting of a dark blue body with "IP-201" imprinted in white ink, and a light blue cap with "20 mg" imprinted in white ink	1 capsule	Capsule shell	

Table 3.2.P.1.2-2 Composition of (b) (4) Capsules 40 mg

Component	Amount per capsule (mg/capsule weight)	Function	Quality Standard
Indomethacin, USP	40.00	Active pharmaceutical ingredient	(b) (4)
Lactose monohydrate	(b) (4)		
Microcrystalline cellulose			
Croscarmellose sodium			
Sodium lauryl sulfate			
Sodium stearyl fumarate			
Total capsule fill weight			
(b) (4) capsule consisting of a dark blue body with "IP-202" imprinted in white ink, and a blue cap with "40 mg" imprinted in white ink	1 capsule	Capsule shell	

2.4 Comments on Novel Excipients

There are no novel excipients in the drug product. The amounts of the excipients used in the drug product as shown in the tables above (b) (4)

2.5 Comments on Impurities/Degradants of Concern

The Applicant referenced DMF (b) (4) for the specification of the drug substance, which is shown below as extracted from the submission.

(b) (4)

Total impurities by HPLC	(b) (4)
Loss on drying	USP <731>
Residue on ignition (%w/w)	USP<281>
Heavy metals	USP <231> Method II
Residual solvents:	

(b) (4)

The acceptance criterion for each indomethacin known related impurities was set at not more than (NMT) (b) (4) based on the ICH qualification threshold. Based on the ICH Q3A guidance, if the drug substance is administered ≤ 2 g/day, the qualification threshold of a drug substance impurity is 0.15% of the drug substance or 1 mg per day intake of the impurity, whichever is lower. In this case, the total intake per day of an impurity is (b) (4) significantly lower than the qualification threshold based on mg amount. The unknown impurities are NMT (b) (4) which is less than the identification threshold required by the ICHQ3A guidance.

For the drug product, the reported impurity levels (NMT) are shown in tables of release specifications and shelf-life specifications of the drug product with same acceptance criteria, as in the table below.

(b) (4)

The impurities in the drug product are regulated according to ICH *Q3B: Impurities in New Drug Products* and are below the required threshold for identification and qualification. As compared to the drug substance, there are no unique impurities produced in the drug product. In addition, all these impurities in the drug product are (b) (4) according to Dr. Xiaobin Shen, the CMC reviewer of this drug product (b) (4)

Of note, the impurities (b) (4) were identified as possessing a structural alert for genotoxicity based on the initial CMC review. If an impurity possesses a structure alert for genotoxicity, qualification is needed even the level of this impurity is below the ICH Q3 qualification threshold. Based the Agency's current policy, computational toxicity assessments are needed for impurity qualification in this situation. For computational toxicology analysis, only Ames is considered because of the large variability and unreliability in the data of other assays. If QSAR for Ames assay is negative, there is no need to further investigate the genotoxicity potential of an impurity ≤ ICH Q3 qualification threshold. However, if QSAR prediction result is positive, further actions are needed. These include 1) decreasing the level of the impurities to an acceptable daily intake level with minimal carcinogenicity concern, or 2) conducting further studies such as Ames assay to investigate the potential genotoxicity. The Applicant submitted computational genotoxicity studies (QSAR analysis) of the 5 known impurities and the results indicated that the all 5 impurities are not genotoxic. However, analysis from the CDER Computational Toxicology Consultation Service for a QSAR analysis of genetic toxicity concluded that (b) (4) are predicted to be positive for mutagenicity in the Ames assay.

Tiforbex is indicated for acute pain and the maximal recommended dose is 120 mg; therefore, the maximal total daily uptake for these impurities are (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 amount of genotoxic impurities may not exceed 120 µg/day for a drug product with < 1 month treatment period. However, the indomethacin drug substance used in Tivorbex has been used in drug products that the Agency approved previously (see details in CMC review for this NDA). Based on the Agency's current policy, the impurities formed in the drug substance is not to be assessed retrospectively if the drug substance is in an approved product and there is no change in the drug substance synthesis. Therefore, this issue was not further pursued.

The Applicant also provided justification for the defined acceptable level of (b) (4) a residual solvent that is not included in ICH Q3C, in the drug substance. This justification report used methods for establishing exposure limits as recommended in ICH Q3C to demonstrate that a daily dose (b) (4) would not likely produce significant toxic effects in human based on available nonclinical information in public domain. This evaluation appears to be appropriate. However, since the drug substance has been used in approved FDA drug products, the level (b) (4) in the drug substance is considered to be acceptable. This justification is not needed for approval of Tivorbex.

2.6 Proposed Clinical Population and Dosing Regimen

Tivorbex is indicated for acute treatment of mild to moderate pain in adults

2.7 Regulatory Background

The sponsor submitted the IND 101,940 for the development of indomethacin submicron capsules. In an advice letter sent to the Sponsor in response to the questions included in the IND submission, the Division stated that "additional nonclinical safety studies are not required to support the safety of indomethacin for an NDA provided clinical exposure to indomethacin is within the approved limits of the RLD". However, the Division indicated that the safety of any novel excipient, as well as any impurities which exceed ICH thresholds must be adequately qualified for safety. Similar information was conveyed to the Sponsor in the EOP2 and pre-NDA meeting.

3 Studies Submitted

3.1 Studies Reviewed

Title	Report Designation	Location
Pharmacokinetics Study Reports		
Indomethacin: A comparative bioavailability study in non-naïve beagle dogs	1609-001	eCTD
Toxicology Study Reports		
Computational assessment and evaluation of potential genotoxicity of 5 indomethacin using MC4PC	11455-21239	eCTD

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

None

4 Pharmacokinetics/ADME/Toxicokinetics

Study Title: Indomethacin: A comparative bioavailability study in non-naïve beagle dogs

Study no.:	1609-001
Study report location:	eCTD
Conducting laboratory and location:	(b) (4)
Date of study initiation:	07/2008
GLP compliance:	Yes
QA statement:	Yes

Non-naïve female beagle dogs at 9 months to 3.5 years of age were used in the study. The experimental design is shown below as extracted from the study report. Mylan Indomethacin tablet 25 mg, and capsules of 25 mg (Indomethacin (b) (4)) or 20 mg (Indomethacin (b) (4)) indomethacin submicron particles were administered orally once on day 1 during the study.

Group Assignments

Group Number	Test Article	Dose Level (mg)	Number of Animals Female
1	Indomethacin IR (Mylan)	25	6
2	Indomethacin (b) (4)	25	6
3	Indomethacin (b) (4)	20	6

Animals were observed for mortality and clinical signs. The body weight was recorded on the day of dosing. Blood samples were collected from all animals via the jugular vein prior to dosing, and post-dosing at 0.25, 0.5, 1, 2, 4, 6, 8, 12, and 24 hours post-dose on Day 1. PK parameters were calculated.

Results:

The dose normalized C_{max} and AUC are shown in the table below. At 20 mg, the indomethacin submicron particle formulation appeared to be similar in Cmax and AUC as compared to the Mylan 25 mg capsule. However, at 25 mg, the indomethacin

submicron particle formulation was lower in Cmax and AUC as compared to the Mylan 25 mg capsule (↓~ 40%).

Comparison of C_{max} and AUC with dosing correction

parameters normalized by dose	Mylan Indomethacin 25 mg capsule	Indomethacin submicron 25 mg capsule	Indomethacin submicron 20 mg capsule
C_{max}/mg (ng/ml)	277	170.8	336
AUC_{0-4hr}/mg (ng•hr/ml)	463	293	478
AUC_{0-24hr}/mg (ng•hr/ml)	1002	606	901

The T_{max} was 1.67, 1.21, and 0.71 hours for Mylan Indomethacin 25 mg capsule, Indomethacin submicron 25 mg capsule, and Indomethacin submicron 20 mg capsule, respectively, suggesting the decrease in indomethacin particles may be associated with a faster absorption.

Overall, this study did not indicate that reduction of indomethacin particle size result in bioavailability increase, but the C_{max} may be reached faster as compared to regular particle size formulation

5 Special Toxicology Studies

Study title: Computational assessment and evaluation of potential genotoxicity of 5 indomethacin degradation products using MC4PC

Study no.:	11455-21239
Study report location:	eCTD
Report date:	August 8, 2012
Conducting laboratory and location:	MultiCASE Inc., Beachwood, OH
GLP compliance:	No

The purpose of this study was to perform a hazard assessment of the potential genotoxicity of five known impurities identified in indomethacin drug substance and drug product. (b) (4)

The structures of these compounds are as follow.

(b) (4)

The assessment was performed with a computer-based expert system consisting of the MC4PC software and 4 sets of carefully designed expert modules, i.e., two sets for rodent carcinogenicity (public domain and proprietary), one set for cardiotoxicity, and one regulatory relevant set for genotoxic potential. The modules were developed by the CTG group of the US FDA with MultiCASE Inc. MC4PC is a knowledge-based system designed to evaluate the associations between the structure of the chemicals and their potential activities in a specific biological assay. Its main goal is to find the structural entities that discriminate active molecules from inactive ones and its success is dependent on the validity of the working hypothesis that a relationship exists between chemical structure and activity. The results of the assessment were summarized in the following table as extracted from the study report. The RCA (Research Cooperative Agreement with FDA) method expert analysis is a protocol currently used to perform human expert prediction of toxicity for test chemicals by processing MC4PC output data and identify structural alerts across multiple toxicologically related endpoints. The process typically involves combining data obtained from a module set consisting of modules representing 3-6 (as many as 20) closely related endpoints. Based on the RCA analysis, all 5 compounds were predicted to be negative in the Ames assay, in vitro gene mutation assay (MA in vitro), in vitro chromosomal assay (CA in vitro), in vivo micronucleus assay (MN in vivo), and in vivo gene mutation assay (MA in vivo). However, (b) (4) were predicted to be positive in the *in vitro* chromosomal assay (CA in vitro); these compounds were identified to contain genotoxic structural alert groups. The conclusion from review experts was inconclusive for the CA in vitro model taking into account all the available evidence. Therefore, it was concluded in this study report that overall, the 5 compounds did not demonstrate convincing evidence of activity in genotoxicity test assessments. Of note, possible structure coverage problems were identified in some of the assessments as indicated below.

Summary of results and overall conclusion for the genotoxicity tests conducted by the Applicant

Compound	Ames		MA *in vitro*		CA *in vitro*		MN *in vivo*		MA *in vivo*		FINAL CONCLUSION
	RCA Method Expert Call	Review Expert	RCA Method Expert Call	Review Expert	RCA Method Expert Call	Review Expert	RCA Method Expert Call	Review Expert	RCA Method Expert Call	Review Expert	
(b) (4)	-	-	-	-	-	-	-	-	-*	-	-
	-I	-	-	-	-	-	-	-	-	-	-
	-	-	-	-	+	?	-	-	-	-	-
	-*	-	-*	-	+*	?	-*	-	-*	-	-
	-*	-	-*	-	+*	?	-*	-	-*	-	-

AMES = bacterial mutation assay; MA = mammalian; CA = chromosomal aberration; MN = mouse micronucleus I - experimentally inactive

+ positive; (+) potentially positive; - negative; (-) potentially negative. ? –inconclusive * possible structural coverage problems

Based on the current thinking of the Agency, only Ames is considered right now for computational toxicology analysis 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. 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, Derek system which uses human expert rules for prediction was also used in the analysis conducted by CTG. (b) (4) were predicted to be negative in mutagenicity. However, (b) (4) were predicted to be positive in mutagenicity based on the results of the prediction in the 3 prediction system.

Results of *in silico* analysis conducted by CDER

(b) (4)

Software	*Salmonella* Mutagenicity
Derek Nexus	I
Model Applier	
CASE Ultra	
Overall Software Prediction	I
Overall Expert Prediction	I

Software	*Salmonella* Mutagenicity
Derek Nexus	NSA
Model Applier	–
CASE Ultra	–
Overall Software Prediction	–
Overall Expert Prediction	–

(b) (4)

Software	*Salmonella* Mutagenicity
Derek Nexus	NSA
Model Applier	–
CASE Ultra	–
Overall Software Prediction	–
Overall Expert Prediction	–

Software	*Salmonella* Mutagenicity
Derek Nexus	+
Model Applier	–
CASE Ultra	Eqv
Overall Software Prediction	+
Overall Expert Prediction	+

Software	*Salmonella* Mutagenicity
Derek Nexus	+
Model Applier	–
CASE Ultra	–
Overall Software Prediction	+
Overall Expert Prediction	+

[1] + = positive; – = negative; Eqv = equivocal; NSA = no structural alerts are identified by DX (Derek Nexus cannot differentiate between a negative call and the inability to make a call because of no coverage); NC = test chemical features are not adequately represented in the model training data set, leading to a no call; I = determined to be negative in laboratory testing; A = determined to be positive in laboratory testing.

Of note, the analysis from the CTG group was conducted based on only dataset of salmonella bacterial strains. E. coli strain models were not included. This is because the currently available E. coli models are based on small training sets and are not very useful.

6 Literature submission

The Applicant conducted nonclinical literature search using National Library of Medicine (NLM, PUBMED) as the search engine with publication period from 1978 - 2012. The publications which were found by literature search are listed in Appendix 1. Since the safety of Tivorbex is covered in dosage and duration by the referenced FDA-approved drug product, Indocin, these publications are not needed to support the safety of Tivorbex. In addition, no fundamentally new information is contained in these publications that is relevant for the Tivorbex label; these publications were not formally evaluated.

7 Appendix/Attachments

List of publications submitted by the Applicant

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/s/

ZENGJUN XU
01/18/2014

ADAM M WASSERMAN
01/20/2014
I concur with the recommendation for approval from the nonclinical perspective.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 204-768 **Applicant: Iroko Pharmaceutical, LLC** **Stamp Date: 04/30/2013**

Drug Name: (b) (4) Capsule (Indomethacin) **NDA/BLA Type: 505 (b)(2)**

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

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	√		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	√		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	√		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	√		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	NA		No animal toxicity studies are required for the approval of this drug product
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	√		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	NA		No animal toxicity studies are required for the approval of this drug product
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	√		

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	√		Human dose multiples were not included in the description of nonclinical studies. However, it is not considered an issue which needs to inform the Applicant in the 74-day letter. The human dose multiples can be easily added during the labeling negotiation
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	√		
11	Has the applicant addressed any abuse potential issues in the submission?	NA		
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?		X	This NDA is not to support a Rx to OTC switch

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? _____yes___

If the NDA/BLA is not fileable from the pharmacology/toxicology 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. None

Z. Alex Xu 06/26/2013
Reviewing Pharmacologist Date

Adam Wasserman 06/26/2013
Team Leader/Supervisor Date

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/s/

ZENGJUN XU
06/26/2013

ADAM M WASSERMAN
06/27/2013