CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211210Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA:	211210
Submission Date:	December 21st 2017
Relevant IND(s):	104140
Submission Type; Code:	505 (b) (2)
Reference Drug:	Mobic® (meloxicam) Tablets (NDA 0209384)
Brand Name:	(b) (4)
Generic Name:	Meloxicam
Formulation; Strength(s):	Orally disintegrating tablet (ODT); 7.5 mg and 15 mg
Clinical Pharmacology Reviewer:	Deep Kwatra, Ph.D.
Clinical Pharmacology Team Leader:	Yun, Xu, Ph.D.
Pharmacogenomics Reviewer:	Oluseyi Adeniyi, Ph.D.
Pharmacogenomics Team Leader:	Christian Grimstein, Ph.D.
OCP Division:	Division of Clinical Pharmacology II
OND Division:	Anesthesia Analgesia and Addiction Products
Sponsor:	TerSera Therapeutics LLC
Proposed Indication:	For the relief of the signs and symptoms of osteoarthritis (OA), rheumatoid arthritis (RA), and pauci-articular or polyarticular course juvenile rheumatoid arthritis (JRA) in patients who weigh ≥ 60 kg
Proposed Dosage Regimen:	Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals. **OA and RA:** Starting dose: 7.5 mg once daily Dose may be increased to 15 mg once daily **JRA:** 7.5 mg once daily in children ≥60 kg

TABLE OF CONTENTS

1.0 Executive Summary

1.1 Recommendation

From the Clinical Pharmacology perspective, NDA 211210 submitted on 12/21/2017 is acceptable. Labeling negotiation with the Applicant was still ongoing when this review was being documented in DARRTS.

1.2 Phase 4 Commitments

None

1.3 Summary of Clinical Pharmacology Findings

TerSera Therapeutics LLC submitted a 505 (b) (2) application for (b) (4) tablets, Orally disintegrating tablet (ODT), 7.5 mg and 15 mg, formulation of meloxicam for the relief of the signs and symptoms of osteoarthritis (OA), rheumatoid arthritis (RA), and pauci-articular or polyarticular course juvenile rheumatoid arthritis (JRA) in patients who weigh ≥ 60 kg. Mobic (NDA-020938, Boehringer Ingelheim Pharmaceuticals Inc) is the listed drug for this 505(b)(2) application. The applicant did not conduct any Phase 3 safety and efficacy studies. As a 505(b)(2) NDA, for establishing the clinical bridge, TerSera conducted a Relative Bioavailability Study (fasting) with to be marketed (TBM) formulation Meloxicam ODT Formulation (15 mg) against Mobic 15 mg IR tablets (Study 10943701). The sponsor also conducted a Relative Bioavailability Study of a Meloxicam ODT TBM Formulation (15 mg) under Fed and Fasted Conditions (Study 10943702) to satisfy the food effect requirements of the formulation. The sponsor also intends to rely on relevant safety and efficacy results from the published literature and the public domain.

The dose strengths for (b) (4) oral tablets are 7.5 and 15 mg that are compositionally proportional. The sponsor proposed dosing regimen of once daily for either strengths. The proposed dosing regimen for both strengths is similar when compared to reference Mobic 7.5 and 15 mg tablets, which are both dosed once daily.

Mobic (meloxicam) IR oral tablets were originally approved on Thursday, April 13th 2000. Since then another dosage form in the form of Oral Suspension (NDA-021530) was also approved in 2004. VIVLODEX tablets (b) (4) (b) (4) were approved in 2015 for 5 mg or 10 mg strengths.

For this NDA, a Pre-NDA meeting was held on March 3rd 2017, under IND 104140. The clinical development program includes two clinical pharmacology studies with TBM formulation (reviewed) and two clinical pharmacology studies with pilot formulation (not reviewed) in order to establish comparative bioavailability to the currently approved meloxicam product, Mobic® and to support of the established efficacy and safety profile of meloxicam. The sponsor also did literature search to supplement clinical pharmacology information in the Mobic product label regarding the mechanism of action (MOA), metabolism, drug-drug-interactions (DDI), and special populations. The objectives of these searches were to identify any new data regarding the (1) MOA; (2) metabolism; (3) potential for DDIs; and (4) special populations that impact the variability

of the pharmacokinetics (PK) of meloxicam. Out of all the publications submitted, only publications related to genomic polymorphisms resulting in altered exposure of meloxicam in poor metabolizers of CYP2C9 were reviewed as the rest of the literature did not add any new information to the Mobic® label.

1.3.1 Clinical Pharmacology Studies:

Two pilot (CB081206, C09173) and 2 pivotal (10943701, and 10943702) Phase 1 studies were conducted for this application. Out of these studies, CB081206 and C09173 PK studies were conducted with initial proof of concept formulations for the sponsor's internal decision making and hence not reviewed. The studies 10943701, and 10943702 were conducted with commercial scale formulation that fulfills the clinical pharmacology information of the proposed product from regulatory requirement perspective.

Phase 1 Studies (with commercial scale formulation):

- Study 10943701: Relative Bioavailability Study of Meloxicam ODT Formulation (15 mg) Versus Mobic (15 mg).
- Study 10943702: Relative Bioavailability Study of Meloxicam ODT Formulation (15 mg) under Fed and Fasted Conditions (Food Effect Study)

Phase 1 Studies (with Pilot formulation):

- Study CB081206: Pilot Relative Bioavailability Study of Meloxicam OTC (15 mg) Versus Mobic (15 mg).
- Study C09173: Pilot Relative Bioavailability Study of Two Meloxicam OTC Formulations (15 mg) Versus Mobic (15 mg)

1.3.2 Clinical Studies:

- The sponsor did not conduct any Phase-III efficacy or safety studies

1.3.3 Relative bioavailability of (b) (4) Tablets (15 mg) compared to reference meloxicam tablets (Study 10943701):

The relative BA of (b) (4) Tablets (15 mg) was compared to meloxicam 15 mg tablets as a part of the study MELl-12-04, under fasting conditions in 32 healthy subjects.

- Relative bioavailability of meloxicam was compared between (b) (4) following a single 15 mg dose to that after a single dose of Mobic 15 mg tablets in fasting healthy subjects. Both resulted in similar systemic exposure and Bioequivalence was established.
- Bioequivalence was established with these 2 products for maximal observed plasma concentration (Cmax), area under the plasma concentration time curve from time 0 to last measurable concentration (AUC0-t), and AUC from time 0 to infinity (AUC0-∞).

- There were no significant differences in elimination half-life ($t_{1/2}$) between [(b) (4)] tablet and Mobic tablets ([(b) (4)] 21.82 hours vs. Mobic tablets 22.13 hours) as well as time to maximum plasma concentration (T_{max}) between the two formulations ([(b) (4)] 4.34 hours vs. Mobic tablets 4.53 hours).

1.3.4 Dose Proportionality between 7.5 and 15 mg [(b) (4)] Tablets:

- The dose proportionality between the two formulations were not studies in a dedicated study by the sponsor but instead the sponsor submitted a request for a waiver.
- The information provided in the biowaiver request includes:
  - The bioavailability of meloxicam and demonstration of bioequivalence of 15 mg meloxicam ODT to Mobic;
  - Demonstration of linear PK between the 7.5 mg and 15 mg strengths, as described in the Mobic package insert;
  - Compositional proportionality between the 7.5 mg and 15 mg strengths; [(b) (4)]
- Based on the review by the Division of Biopharmaceutics the a biowaiver for conducting dose proportionality studies can be granted.

1.3.5 Food Effect on [(b) (4)]

The food effect was assessed for [(b) (4)] 15 mg Tablets in 28 (Fasted) and 28 (Fed) healthy subjects, respectively.

- When taken under fed conditions, bioequivalence was established for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ compared to fasted conditions.
- Taking [(b) (4)] with food results in significantly increased the median time to maximal plasma concentration (T_{max}) from 4.0 hours (fasted) to 13.0 hours (fed). The delayed Tmax under fed condition may affect onset of action for the product, which will be clinically relevant for an acute pain indication. However, since this product is for chronic use, its impact will not be considered significant if the steady state PK profiles are comparable between fed and fasted conditions.
- Under fed conditions, the reference Mobic tablet results in 22% higher Cmax and no change in AUC compared to fasted conditions. Taking Mobic tablets with food resulted in Tmax achieved between 5 and 6 hours. The source of reference food effect data is from the label of the reference drug.
- Since meloxicam is a chronic use drug, steady state exposure prediction was made to compare the steady-state meloxicam PK profiles after the administration of Mobic (15 mg) and [(b) (4)] (15 mg) when given under fed and fasted conditions. Overall, the results showed that [(b) (4)] given at 15 mg QD produces a meloxicam PK profile within the range of Mobic 15 mg QD under both fed and fasted conditions

1.3.6 OSI Inspection:

Since the NDA relied on the pivotal BE study to establish the scientific bridge to the Mobic tablets, and onsite inspection was requested from the OSI for the study 10943701

- The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection.
- The Rationale for this recommendation was that OSIS recently inspected the sites for the pivotal BE study. The inspectional outcome from the inspections was classified as No Action Indicated (NAI)

1.3.7 Pharmacogenomics Information:

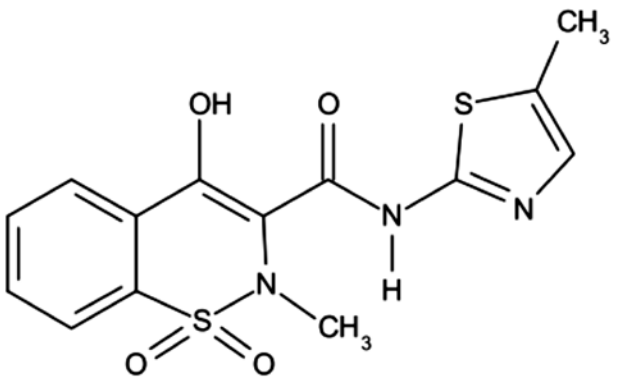
Sponsor submitted data to suggest that Meloxicam systemic exposure and pharmacodynamic (PD) responses are higher in subjects of the poor metabolizer genotypes such as CYP2C9*3 genotypes compared to subjects of the extensive metabolizer CYP2C9*1 genotype. The sponsors were not able to reach the authors to get the raw data regarding the publications of pharmacokinetics for meloxicam in individuals with different polymorphisms for CYP2C9. Due to the lack of patient level raw PK data as well as detailed information regarding bioanalytical methods used, there is not sufficient confidence to make a dosing recommendation within the label. But this information is still qualitatively important and hence will be put in the label for the awareness of the broader medical community. The details of the Pharmacogenomic information provided and the recommendations regarding the labeling language is presented in the Pharmacogenomics review in the Appendix section.

Overall, adequate information has been provided characterizing the clinical pharmacology aspects of (b) (4) tablets.

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 drug substance, and the formulation of the drug product?

Table 2.1.1: Physical-Chemical Properties of Meloxicam Acid	
Drug Name	Meloxicam
Chemical Name	4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide
Structure	
Molecular Formula	$C_{14}H_{13}N_3O_4S_2$
Molecular Weight	351.4

Formulation:
is a freeze-dried, orally administered formulation containing either 7.5 mg or 15 mg meloxicam and is designed to rapidly disintegrate in the mouth. Both strengths are orange-flavored, yellow, circular tablets debossed with either "7.5" or "15" logos. The strengths are similar to the 7.5 mg and 15 mg strengths of Mobic.

2.1.2 What is the regulatory history of Meloxicam products?

Meloxicam 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: Orange Book Meloxicam products:

Drug name and Application #	Dosage form/Route	Strength	Company
N207233	CAPSULE	5MG	IROKO PHARMACEUTICALS LLC
N207233	CAPSULE	10MG	IROKO PHARMACEUTICALS LLC
N021530	Suspension;oral	7.5MG/5ML	BOEHRINGER INGELHEIM
A077882	Tablet;oral	15MG	APOTEX INC

A077882	Tablet;oral	7.5MG	APOTEX INC
A078008	Tablet;oral	15MG	AUROBINDO PHARMA
A078008	Tablet;oral	7.5MG	AUROBINDO PHARMA
A077920	Tablet;oral	15MG	BRECKENRIDGE PHARM
A077920	Tablet;oral	7.5MG	BRECKENRIDGE PHARM
A077918	Tablet;oral	15MG	CARLSBAD
A077918	Tablet;oral	7.5MG	CARLSBAD
A077929	Tablet;oral	15MG	CIPLA LTD
A077929	Tablet;oral	7.5MG	CIPLA LTD
A077931	Tablet;oral	15MG	DR REDDYS LABS INC
A077931	Tablet;oral	7.5MG	DR REDDYS LABS INC
A077932	Tablet;oral	15MG	GLENMARK GENERICS
A077932	Tablet;oral	7.5MG	GLENMARK GENERICS
A077944	Tablet;oral	15MG	LUPIN PHARMS
A077944	Tablet;oral	7.5MG	LUPIN PHARMS
A077923	Tablet;oral	15MG	MYLAN
A077923	Tablet;oral	7.5MG	MYLAN
A077938	Tablet;oral	15MG	PURACAP PHARM
A077938	Tablet;oral	7.5MG	PURACAP PHARM
A077928	Tablet;oral	15MG	STRIDES PHARMA
A077928	Tablet;oral	7.5MG	STRIDES PHARMA
A077937	Tablet;oral	15MG	SUN PHARM INDS INC
A077937	Tablet;oral	7.5MG	SUN PHARM INDS INC
A078102	Tablet;oral	15MG	TARO
A078102	Tablet;oral	7.5MG	TARO
A077936	Tablet;oral	15MG	TEVA PHARMS
A077936	Tablet;oral	7.5MG	TEVA PHARMS
A077927	Tablet;oral	15MG	UNICHEM
A077927	Tablet;oral	7.5MG	UNICHEM
A077921	Tablet;oral	15MG	ZYDUS PHARMS USA
A077921	Tablet;oral	7.5MG	ZYDUS PHARMS USA
N020938	Tablet;oral	15MG	BOEHRINGER INGELHEIM
N020938	Tablet;oral	7.5MG	BOEHRINGER INGELHEIM

2.1.3 What is the composition of the to-be-marketed formulation of (b) (4) tablets?

The proposed commercial dosage forms of (b) (4) tablets include (b) (4) mg strengths of Meloxicam. Table 2.1.3 provides the quantitative composition for both capsule strengths and the function of each component.

Table 2.1.3: Composition of (b) (4) tablets 7.5 and 15 mg strengths

Component	Quality Standard	Function	Strength	
			7.5	15
			Quantity per Tablet (mg)	

Meloxicam	USP	Active pharmaceutical ingredient	7.5	15
Gelatin	USP/NF	[redacted]		
Mannitol	USP			
Citric acid [redacted]	USP			
Aspartame[1]	USP/NF			
Orange flavor	In-house			
[redacted]	USP			
	-			
	-			

[1]Amount of phenylalanine (a component of aspartame) is 0.30 mg for the 7.5 mg dose and 0.59 mg for the 15 mg dose
Abbreviations: NA = not applicable; NF = National Formulary; ODT = orally disintegrating tablet; USP = United States Pharmacopeia

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

Meloxicam is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. Like other NSAIDs, the mechanism of action of meloxicam is thought to be related to inhibition of prostaglandin synthetase (cyclooxygenase). The proposed indication for [redacted] tablets is Osteoarthritis (OA), Rheumatoid Arthritis (RA), Juvenile Rheumatoid Arthritis (JRA) Pauciarticular and Polyarticular Course, in patients who weigh ≥60 kg.

2.1.5 What are the proposed dosage and route of administration?

[redacted] tablets are intended for oral administration. The proposed dosage is 7.5 mg or 15 mg once daily same as Mobic.

2.1.6 What is the core studies submitted in this NDA?

The core clinical development program includes two clinical pharmacology studies using the final to-be marketed formulation.

- **Study 10943701**: A Phase 1, single-center, single-dose, randomized, 2-treatment, 2-period, crossover, relative bioavailability study conducted under fasting conditions to compare the PK characteristics of the to-be-marketed meloxicam ODT 15 mg formulation (Catalent UK Swindon [redacted]) with those of the RLD, Mobic 15 mg tablets (Boehringer Ingelheim, Mexico).
- **Study 10943702**: A Phase 1, single-center, single-dose, randomized, 2-treatment, 2-period, crossover, bioavailability study to compare the PK characteristics of to-be-marketed meloxicam ODT 15 mg formulation (Catalent UK Swindon [redacted]) in healthy volunteers under fed and fasted conditions.

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?

As a 505(b)(2) NDA, for establishing the clinical bridge, TerSera conducted a Relative Bioavailability Study (fasting) with to be marketed (TBM) formulation Meloxicam ODT Formulation (15 mg) against Mobic 15 mg IR tablets of NDA-020938 (Boehringer Ingelheim Pharmaceuticals Inc) (Study 10943701). The sponsor also conducted a Relative Bioavailability Study of a Meloxicam ODT TBM Formulation (15 mg) under Fed and Fasted Conditions (Study 10943702) to satisfy the food effect requirements of the formulation. The sponsor also intends to rely on relevant safety and efficacy results from the published literature and the public domain. There were no clinical safety and efficacy studies conducted under this NDA.

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. There were no clinical safety and efficacy studies conducted under this NDA.

2.2.3 What are the general PK characteristics of the drug?

The absorption, distribution, metabolism, and excretion of Meloxicam as a molecular entity are described in the label for the reference listed drug (Mobic 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?

Meloxicam is extensively metabolized in the liver to 4 pharmacologically inactive metabolites. (b) (4) analgesic activity is primarily due to the parent compound Meloxicam; only the parent compound was measured to assess the PK parameters.

2.2.5 What are the characteristics of drug absorption? Are (b) (4) parameters dose proportional?

The absolute bioavailability of meloxicam tablets was 89% following a single oral dose of 30 mg compared with 30 mg IV bolus injection. Following single intravenous doses, dose-proportional pharmacokinetics were shown in the range of 5 mg to 60 mg. After multiple oral doses the pharmacokinetics of meloxicam tablets was dose-proportional over the range of 7.5 mg to 15 mg (per Mobic label). Dose proportionality was not studied for (b) (4) Tablets 7.5 mg and 15 mg doses. The sponsor instead asked for a biowaiver towards conducting clinical studies as per the sponsor the two formulations are dose proportional and have instead submitted the following information:

- The bioavailability of meloxicam and demonstration of bioequivalence of 15 mg meloxicam ODT to Mobic;
- Demonstration of linear PK between the 7.5 mg and 15 mg strengths, as described in the Mobic package insert;
- Compositional proportionality between the 7.5 mg and 15 mg strengths; and

(b) (4)

2.3 Intrinsic factors

2.3.1 Pharmacogenomics

Sponsor submitted data to suggest that Meloxicam systemic exposure and PD responses are higher in subjects of the poor metabolizer genotypes such as CYP2C9*3 (Lee et al. 2014, Zhang et al. 2014, Xu et al. 2001) or CYP2C9*13 (Bae et al. 2011) genotypes compared to subjects of the extensive metabolizer CYP2C9*1 genotype. Results from Bae et al. revealed that after a single 15 mg oral dose of meloxicam, *13 heterozygotes (*1/*13) had a 2.42-fold and 1.46-fold increase in AUC0-∞ and Cmax respectively, when compared to the wild type genotype (*1/*1). In another study, Lee et al. evaluated the impact of the *3 haplotype on the pharmacokinetics and pharmacodynamics of meloxicam. In this study, after a single 15 mg oral dose of meloxicam, *3 homozygotes, i.e. the *3/*3 genotype, had an 8.2-fold increase in AUC and heterozygous subjects with the *1/*3 genotype had a 1.7-fold increase in AUC when compared to subjects with the wildtype i.e. genotype.

Since this data was going to be used in making labeling claim, an IR was sent to the sponsor to provide bioanalytical and Raw PK data for these publications. The following IR was sent: "It appears you intend to rely on literature data to support labeling claims for your product. For all human PK studies you cited and summarized from literature, we are unable to locate the bioanalytical validation/performance data and raw PK data in your NDA submission. We recommend you to contact the authors to obtain these information. As mentioned to you in the pre-NDA meeting due diligence is required to acquire such information about the studies, otherwise you must provide adequate justification that the required information is not obtainable and why the results from the literature can still be used to support your proposed product." The sponsor did the due diligence to contact the authors of the publications for the raw data. They responded that they have not been able to reach the authors to get the raw data regarding the publications of pharmacokinetics for meloxicam in individuals with different polymorphisms for CYP2C9. Due to the lack of patient level raw PK data as well as detailed information regarding bioanalytical methods used there is not sufficient confidence to make a specific dosing recommendation within the label. But this information is still qualitatively important and should be put in the label for the awareness of the broader medical community by placing it in the label.

For greater details on the literature submitted and the underlying results refer to the Pharmacogenomics review by Dr. Oluseyi Adeniyi the Pharmacogenomics reviewer.

2.3.2 What is the pediatric plan?

Pediatric Study Plan (PSP) (b) (4) for treatment of osteoarthritis pain states that development of a pediatric formulation, the conduct of non-clinical studies, pediatric pharmacokinetic studies, and clinical effectiveness and safety studies are "not applicable." Based on this, they intended to seek a waiver from the requirements of the Pediatric Research Equity Act (PREA) in the NDA submission for the proposed indication. The initial PSP contained the "Request for Waiver from Pediatric Research Equity Act," based on the finding that pediatric "studies are impossible or highly impractical (section 505B(a)(4)(B)(i) of the Act)" in the proposed indications.

Reviewer comments:
The initial PSP for (b) (4) *was reviewed and the agency agreed with the sponsor's intent to not conduct studies in pediatric subjects and to request a full waiver from conducting pediatric studies in all pediatric age groups based on the finding that pediatric studies are impossible or highly impractical in the proposed indication.*

2.4 General Biopharmaceutics

2.4.1 What is the relative bioavailability of (b) (4) tablets compared to the reference drug, Meloxicam Tablet?

The relative bioavailability of (b) (4) 15 mg tablets was compared to reference Meloxicam 15 mg Tablets (Mobic) under fasted conditions as a part of Study 10943701. This study was done using commercial scale formulation (b) (4) This was a GLP-compliant, single-center, single-dose, randomized, 2-treatment, 2-period, crossover, relative bioavailability study conducted under fasting conditions. A total number of 32 healthy subjects were randomized to the two treatments; however, 1 subject had plasma meloxicam concentrations greater than 5% of C_{max} at the start of Period II and was excluded from the PK analysis. The remaining 31 subjects are included in the PK summaries.

Treatments:

- **Reference A:** a single 15 mg dose of to-be-marketed meloxicam ODT formulation (Batch No. 1024674) placed on the tongue which was swallowed after the tablet was completely dissolved.
- **Reference B:** a single oral dose of Mobic tablet given with 240 mL water. Both treatments were administered under fasting conditions.

There was a 7-day washout period between treatments, which was considered adequate based on a meloxicam t½ of 20 to 24 hours. Blood samples were taken within 1 hour before dosing through 72 hours after dosing for measurement of plasma meloxicam concentrations.

Results:
The plasma concentration-time profiles comparing (b) (4) ODT 15 mg tablets and meloxicam 15 mg IR tablets under fasted conditions are shown in figures 2.4.1a and 2.4.1b. 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:

- Relative bioavailability of meloxicam was compared between [(b) (4)] following a single 15 mg dose to that after a single dose of Mobic 15 mg tablets in fasting healthy subjects. Both resulted in similar systemic exposure and Bioequivalence was established.
- Bioequivalence was established with these 2 products for maximal observed plasma concentration (Cmax), area under the plasma concentration time curve from time 0 to last measurable concentration (AUC0-t), and AUC from time 0 to infinity (AUC0-∞).
- There were no significant differences in elimination half-life ($t_{1/2}$) between [(b) (4)] tablet and Mobic tablets ([(b) (4)] 21.82 hours vs. Mobic tablets 22.13 hours) as well as time to maximum plasma concentration (T_{max}) between the two formulations ([(b) (4)] 4.34 hours vs. Mobic tablets 4.53 hours).

Figure 2.4.1a: Mean meloxicam plasma concentration-time profiles after administration of [(b) (4)] tablet (15mg) and mobic tablet (15mg) under fasted conditions.

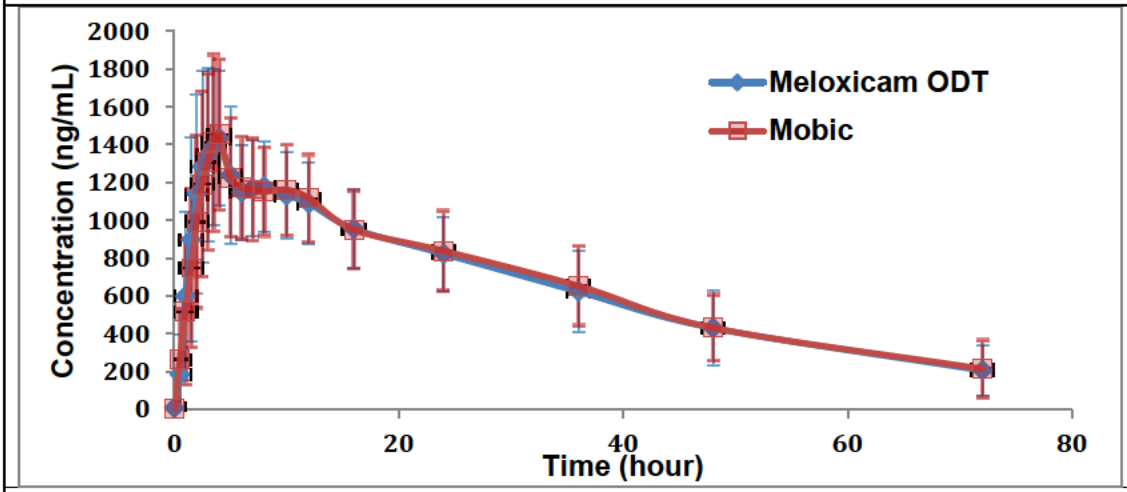


Figure 2.4.1b: Semilog Plot of Mean meloxicam plasma concentration-time profiles after administration of [(b) (4)] tablet (15mg) and mobic tablet (15mg) under fasted conditions.

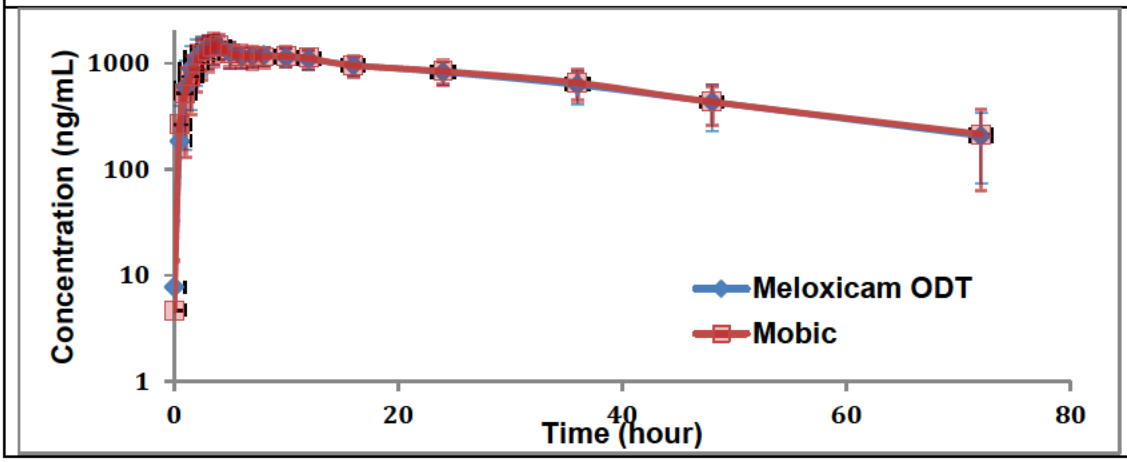


Table 2.4.1a. Pharmacokinetic parameters comparing [(b) (4)] tablets and mobic tablets under fasted conditions.

Parameter	Arithmetic mean ± SD (%CV) (n = 31)	
	[(b) (4)] tablets Fasted (15mg)	Mobic tablets (15 mg) Fasted
Cmax (ng/mL)	1492.7419 ± 390.7809 (26.1787)	1513.0968 ± 401.8663 (26.5592)
AUC_{0-t} (hr*ng/mL)	46000.0048 ± 11970.7825 (26.0234)	39093.8±16500.2
$AUC_{0-\infty}$ (hr*ng/mL)	53230.8917 ± 15486.9153 (29.0938)	40875.6±11733.5
Tmax (hr)*	4.3409 ± 2.7059 (62.3350)	4.5328 ± 2.6359 (58.1510)
$T_{1/2}$ (hr)	21.8207 ± 5.2126 (23.8883)	22.1354 ± 6.9664 (31.4718)

*Median (min, max);

Table 2.4.1b: Geometric LS mean ratios and 90% confidence intervals for Cmax, AUC_{0-t} and $AUC_{0-\infty}$ of [(b) (4)] (15 mg) versus mobic tablets (15 mg) in fasted conditions.

Parameter	Geometric LS mean		Geometric LS mean ratio (90% CI of ratio) [(b) (4) 15 mg / Mobic 15 mg]
	[(b) (4)] (15 mg)	Mobic (15 mg)	
Cmax (ng/mL)	1447.18	1461.99	0.9899 (0.9395, 1.0430)
AUC_{0-t} (ng.h/mL)	44485.24	45227.92	0.9836 (0.9546, 1.0135)
$AUC_{0-\infty}$ (ng h/mL)	50001.55	51350.53	0.674 (0.9313, 1.0181)

2.4.2 What is the effect of food on the BA of [(b) (4)] in comparison to the mobic tablets?

The food effect was assessed for [(b) (4)] 15 mg tablets in Fasted and Fed healthy subjects, respectively. This study was done using commercial scale formulation of [(b) (4)]. This was a GLP-compliant, single-center, single-dose, randomized, 2-treatment, 2-period, crossover, bioavailability study to compare the PK characteristics of to-be-marketed meloxicam ODT 15 mg formulation (Catalent UK Swindon [(b) (4)]) in healthy volunteers under fed and fasted conditions. A total number of 32 healthy subjects were randomized to the two treatments. In total, 30 subjects completed all study periods (i.e., received IMP under both fed and fasted conditions). Two subjects voluntarily withdrew, and 2 subjects had Period II pre-dose plasma meloxicam levels greater than 5% of the measured C_{max} and were excluded from the PK analysis. A total of 28 subjects were included in the PK analysis.

Treatments:

- **Test A:** a single 15 mg dose of to-be-marketed meloxicam ODT formulation (Batch No. 1024674) placed on the tongue which was swallowed after the tablet was completely dissolved following a high-fat standardized breakfast.
- **Reference B:** a single 15 mg dose of to-be-marketed meloxicam ODT formulation (Batch No. 1024674) placed on the tongue which was swallowed after the tablet was completely dissolved after at least a 10 hour overnight fast.

The standardized high-fat breakfast consisted of 2 eggs fried in butter, 2 strips of bacon, 4 oz hash brown potatoes, 2 slices of toast with butter, and 8 oz whole milk. The breakfast contained 150 calories from protein, 250 calories from carbohydrates, and 500 calories from fat. There was a 7-day washout period between treatments, which was considered adequate based on a meloxicam t½ of 20 to 24 hours. Blood samples were taken within 1 hour before dosing through 72 hours after dosing for measurement of plasma meloxicam concentrations. The study sample size was adequately powered to demonstrate bioequivalence.

Results:

The Figures 2.4.2a and 2.4.2b show the plasma concentration-time profiles of (b) (4) 15 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 C_{max} for meloxicam are presented in Table 2.4.2a and Table 2.4.2b. The summary of results is shown below:

- When taken under fed conditions, (b) (4) tablets results in decreased rate (T_{max}) but not the overall extent of meloxicam absorption (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$).
- Under fed conditions, (b) (4) 15 mg tablets results in 7% lower C_{max}, 4% higher AUC_{0-t} and no change in $AUC_{0-\infty}$ respectively compared to the fasted conditions and the 90% confidence intervals were well within 80 to 125%. Taking (b) (4) with food delayed the Tmax by 9 hours (4 hours fasted vs. 13 hours fed).
- Under fed conditions, the reference Mobic tablets results in 22% higher Cmax no change in AUC compared to fasted conditions. Taking mobic tablets with food resulted in Tmax achieved between 5 and 6 hours. The source of reference food effect data is from the label of the reference drug.
- Since meloxicam is a chronic use drug, steady state exposure prediction were made to compare the steady-state meloxicam PK profiles after the administration of Mobic (15 mg) and (b) (4) (15 mg) when given under fed and fasted conditions. Overall, the results showed that (b) (4) given at 15 mg QD produces a meloxicam PK profile within the range of Mobic 15 mg QD under both fed and fasted conditions. The initial results achieved by the sponsor are presented in figure 2.4.2c.

Figure 2.4.2a: Mean meloxicam plasma conc.-time profiles for 15 mg (b) (4) tablets under fasted and fed conditions (Study 10943702)

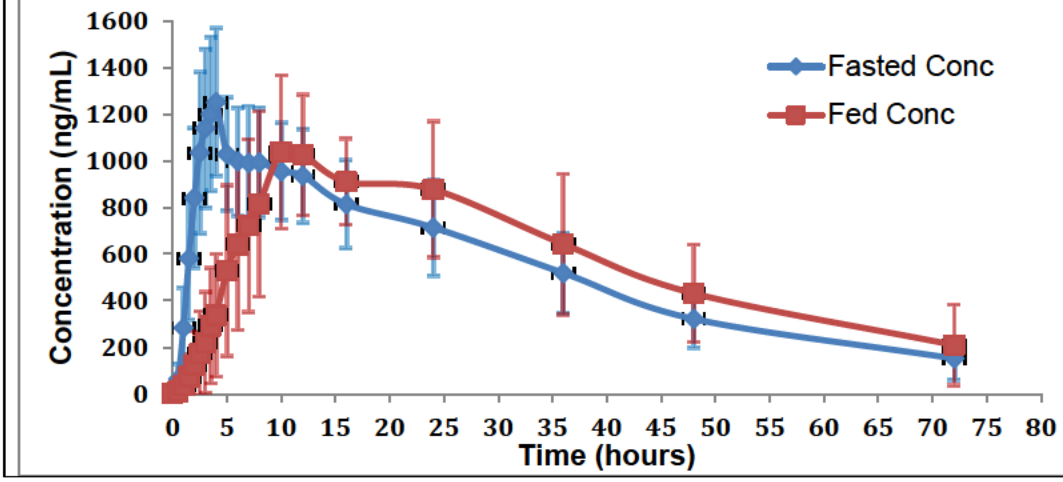


Figure 2.4.2b: Semilog Plot of Mean meloxicam plasma conc.-time profiles for 15 mg (b) (4) tablets under fasted and fed conditions (Study 10943702)

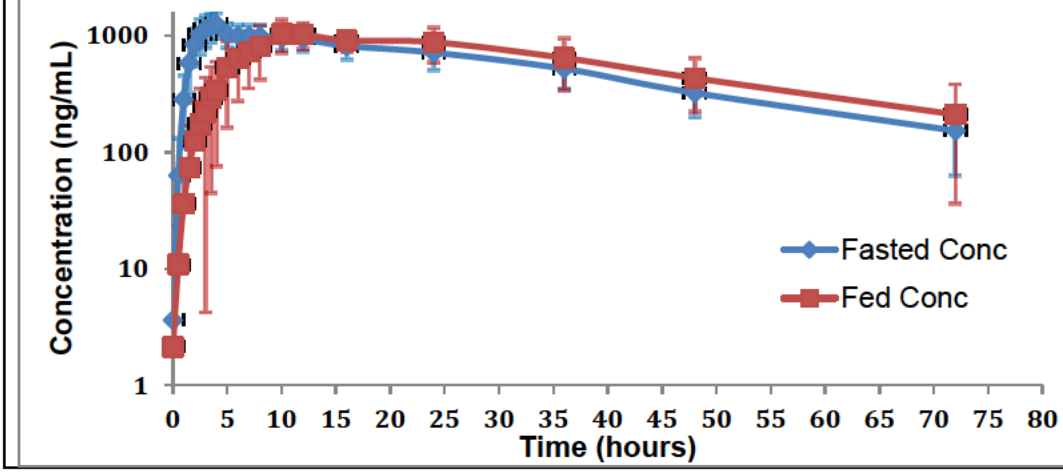


Table 2.4.2a. Pharmacokinetic parameters of meloxicam after administration of (b) (4) tablets under fasted and fed conditions

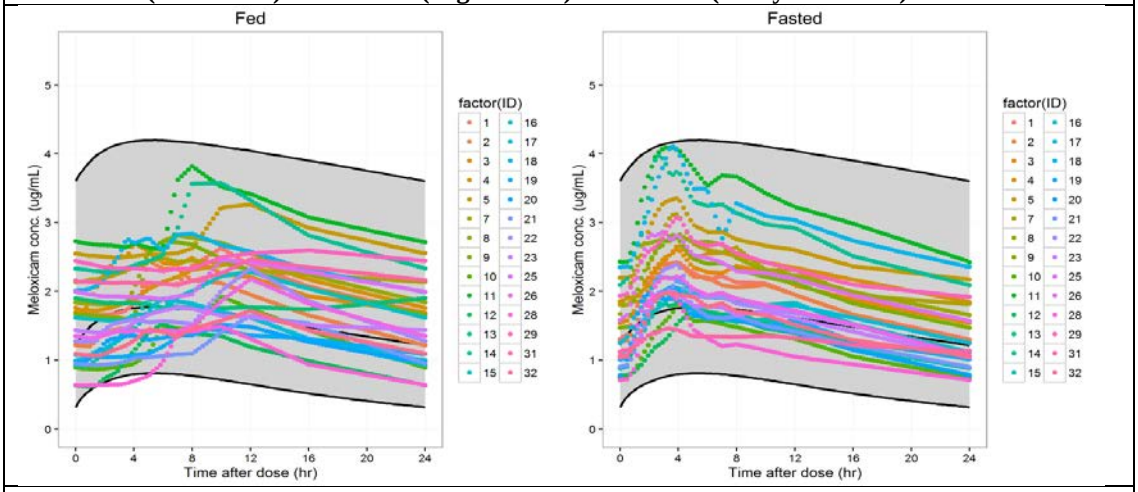
Parameter	(b) (4) Geometric Mean ± SD (%CV) (Study 10943702)	
	Fed	**Fasted**
Cmax (ng/mL)	1165.2857 ± 216.2762 (18.5599)	1277.0714 ± 326.2725 (25.5485)
AUC_{0-t} (hr*ng/mL)	39202.0426 ± 9702.6902 (24.7505)	38454.5975 ± 10773.7923 (28.0169)
$AUC_{0-\infty}$ (hr*ng/mL)	44657.2345 ± 13666.2197 (30.6025)	44008.5826 ± 13782.7570 (31.3183)
Tmax (hr)	13.0744 ± 7.6828 (58.7621)	3.6964 ± 0.5667 (15.3298)
$T_{½}$ (hr)	20.4477 ± 6.1560 (30.1059)	21.6444 ± 7.9520 (36.7395)

Table 2.4.2b: Ratio of geometric LS means and 90% CI of AUC and Cmax comparing [redacted] tablets under fasted and fed conditions.

PK parameter	Treatment Ratio (90% CI of ratio)
	[redacted] **Fasted /** [redacted] **Fed**
Cmax	0.9378 (0.8585, 1.0244)
AUC_{0-t}	1.0406 (0.9538, 1.1353)
$AUC_{0-\infty}$	0.9923 (0.9558, 1.0302)

The Mobic label states that it can be administered without regard to timing of meals. The observed food effect for [redacted] tablets is not comparable to the reference meloxicam tablets, even though significant changes were not observed in the overall exposure the significant delay in T_{max} was a concern. To alleviate the concern, the sponsor compared the superposition using the observed single-dose concentration data in 28 subjects from Study 10943702 of their product to the simulated steady-state concentrations with Mobic 15 mg QD under mixed meal conditions derived from literature. The results (Figure 2.4.2c) showed that the exposures of the sponsors product at steady state were well within the exposures observed with Mobic but since this was a cross study comparison, an information request (IR) was sent to the sponsor. The following IR was sent to the sponsor: "*We observe that you have compared the superposition using the observed single-dose concentration data in 28 subjects from Study 10943702 of your product to the simulated steady-state concentrations with Mobic 15 mg QD under mixed meal conditions derived from literature, which is a cross study comparison. Since bioequivalence on AUC and C_{max} has been met between your product in fasted and fed state, conduct simulation to compare the steady state exposures of your product in the fasted and fed state to avoid cross study comparisons. You may also compare steady state PK of your product in fasted state to that of Mobic in fasted state based on your own study data for further strengthening your argument that the steady-state exposures will be similar and hence the delayed T_{max} should not be an issue. Submit data by within two months of receiving this request.*"

Figure 2.4.2c: Simulated Steady-State Profiles for Mobic 15 mg QD Overlaid with the Superposition Results from the 28 Subjects (Study 10943702) Dosed with Meloxicam ODT 15 mg Under Fed (Left Panel) and Fasted (Right Panel) Conditions (Study 10943703)



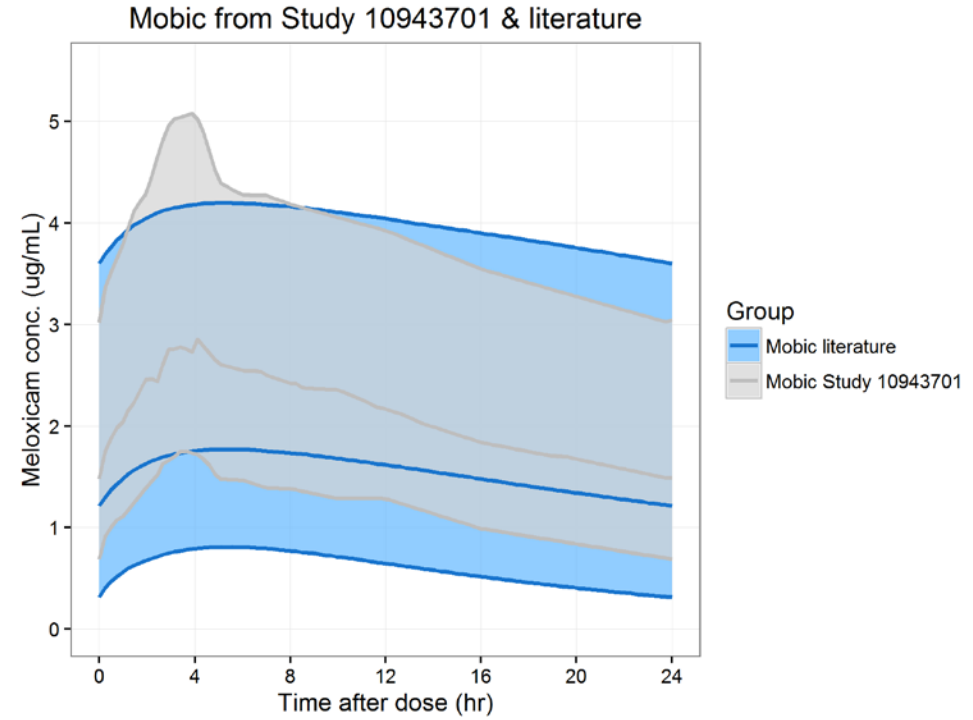
Colored dots: steady-state concentrations with Meloxicam ODT 15 mg QD, based on superposition using the

observed single-dose concentration data in 28 subjects from Study 10943702. Black lines: the 2.5th, 50th, and 97.5th percentiles of the simulated steady-state concentrations with Mobic 15 mg QD under mixed meal conditions. Shaded area: 95% prediction interval of the simulated steady-state profile**.**

In response to the IR the sponsor agreed to the following:
1) Comparison of the superposition simulated steady-state concentrations of Meloxicam ODT 15 mg in the fed and fasted state using the data from Study 10943702.
2) Comparison of the superposition simulated steady-state concentrations of meloxicam in the fasted state utilizing Mobic and Meloxicam ODT data from the pivotal bioequivalence (BE) study (Study 10943701).
3) Comparison of the popPK Mobic simulations (from literature) under mixed meal conditions with the Mobic superpositions from the pivotal BE study (Study 10943701) under fasted conditions, to further validate the analysis that was previously conducted.

Reviewers Comments: *The results of these new simulations, especially of those comparing the Mobic exposures of their own study with literature (figure 2.4.2d) when taken along with the results of the relative bioavailability study (10943701) showing that Mobic and* (b) (4) *are bioequivalent indicate that at steady state the exposures of the sponsors product and reference would not be significantly different. The chronic indication of the drug along with the results of the simulation indicate that the delay in* T_{max} *will not result in alteration in efficacy and hence* (b) (4) *can also be labeled same as Mobic to be taken without regards to food.*

Figure 2.4.2d: Simulated PopPK Steady-State Profiles for Mobic 15 mg QD Under Mixed Meal Conditions (from Literature) Overlaid with the Superposition Results from the 31 Subjects (Study 10943701) Dosed with Mobic 15 mg under Fasted Conditions



Lines: 2.5th, 50th, and 97.5th percentiles of the superposition simulated steady-state concentrations. Shaded area: 95% prediction interval of the superposition simulated steady-state concentrations.

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:
Novum Pharmaceutical Research Services, Wilcrest Green Office Park, 3320 Walnut Bend Lane, Houston, TX 77042-4712.

- Clinical study 10943701 began dosing on 03/02/10 and was completed on 03/12/10.
- Clinical study 10943701 began dosing on 03/06/10 and was completed on 03/16/10

Bio-analytical Facility:
(b) (4)
Samples were collected and provided to (b) (4) in support of Novum Pharmaceutical Research Services Protocols 10943701 and 10943702 for bioanalysis. The plasma concentrations of Meloxicam were analyzed using validated LC-MS/MS assays. The samples for the pilot studies were analyzed in a different facility (b) (4) (b) (4) The summary if bioanalytical method validation is presented in Table 2.5.1 for both the bioanalytical facilities.

Table2.5.1: Summary of Analytical Methods for Quantification of Meloxicam in Human Plasma:

Method	(b) (4)	(b) (4)
Report No.	BL-MVR-018	DCN 11-859-V3
Method No.	BL-MS-018-00	ATM-888
Method	LC-MS/MS	LC-MS/MS
Matrix	plasma	plasma
Clinical Studies Supported	CB081206, C09173	10943701 and 10943702
Standard Curve Range	5.045 to 2001.996 ng/mL	5.00 to 3000 ng/mL
QC Samples	14.286, 199.081, 829.506, and 1595.203 ng/mL	15.0, 600, and 2400 ng/mL with dilution QC of 15,000 ng/mL
Linearity	Slope = 0.0154 to 0.0164, Intercept = 0.00807 to 0.0235, R2≥0.9980	Slope = 0.000504; Intercept = 0.000504; R2 = 0.9973

Accuracy of LLOQ	Intra-day: 84.81 % to 103.10% Inter-day: 93.34%	Intra-day: -5.6% to 13.8% Inter-day: 5.8%
Precision of LLOQ	Intra-day: 4.27% to 10.13% Inter-day: 10.89%	Intra-day: 3.6% to 13.1% Inter-day: 11.9%
Accuracy of low, mid, and high QCs	Intra-day: 91.46% to 105.78% Inter-day:92.98% to 105.33%	Intra-day: -9.8% to 10.0% Inter-day: -5.3% to 1.3%
Precision of low, mid, and high QCs	Intra-day: 0.63 to 3.06 Inter-day: 1.68% to 2.82%	Intra-day: 1.7% to 12.1% Inter-day: 6.1% to 10.3%
Freeze-thaw stability	4 cycles at -28ºC ± 5ºC	5 cycles
Table-top stability	6 hours 14 minutes at room temperature	Room temperature for 24 hours
Long-term stability	NA	104 days

3.0 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. Labeling negotiation with the Sponsor is still ongoing when this review is documented in Darrts.

Reviewer Comments:

This labeling recommendation for Pharmacogenomics for (b) (4) is updated in comparison to previous Meloxicam products. The updated section is in 12.3. These recommendations are due to new literature submitted by the sponsor with regards to difference if PK observed in patients with different CYP2C9 polymorphisms.

7 Drug Interactions

CYP2C9 inhibitors	
Clinical Impact:	• In vitro studies indicate that CYP2C9 (cytochrome P450 metabolizing enzyme) plays an important role in this metabolic pathway with a minor contribution of the CYP3A4 isozyme. Thus concomitant usage of CYP2C9 inhibitors (such as amiodarone, fluconazole, and sulphaphenazole) may lead to abnormally high plasma levels of meloxicam due to reduced metabolic clearance.
Intervention:	Consider dose reduction in patients undergoing treatment with CYP2C9 inhibitors, and monitor patients for adverse effects.

8 Use in Specific Populations

8.8 Poor Metabolizers of CYP2C9 Substrates:

In patients who are known or suspected to be poor CYP2C9 metabolizers based on genotype or previous history/experience with other CYP2C9 substrates (such as warfarin and phenytoin) consider dose reduction as they may have abnormally high plasma levels due to reduced metabolic clearance, and monitor patients for adverse effects.

12.2 Pharmacokinetics

Food and Antacid Effects

(b) (4)

12.3 Pharmacogenomics

CYP2C9 activity is reduced in individuals with genetic variants (b) (4) such as CYP2C9*2 and CYP2C9*3 alleles. Limited data from 3 published reports showed that (b) (4)

[redacted]

[redacted]-meloxicam AUC was substantially higher in individuals with reduced CYP2C9 activity, particularly in poor metabolizers (e.g., *3/*3), compared to normal metabolizers (*1/*1). [redacted] The frequency of CYP2C9 poor metabolizer genotypes varies based on racial/ethnic background but is generally present in <5% of the population.

4.0 Appendices

4.1 Sponsor's Proposed Label

32 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

4.2 Pharmacogenomics Review

Background

The applicant proposed the addition of section 12.5 in the proposed label for meloxicam. The current labeling for meloxicam as approved does not include a section 12.5. The applicant's proposed addition is italicized below.

> *CYP2C9 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity, such as* (b) (4) *CYP2C9*2 and CYP2C9*3 polymorphisms.* (b) (4)

Submission Contents Related to Genomics

The proposed labeling change is based on a review of the literature on the impact of CYP2C9 polymorphisms on the pharmacokinetics of meloxicam in the following three studies.

- Bae, J. W., Choi, C. I., Jang, C. G., & Lee, S. Y. (2011). Effects of CYP2C9 *1/*13 on the pharmacokinetics and pharmacodynamics of meloxicam. *British journal of clinical pharmacology*, *71*(4), 550-555.
- Lee, H. I., Bae, J. W., Choi, C. I., Lee, Y. J., Byeon, J. Y., Jang, C. G., & Lee, S. Y. (2014). Strongly increased exposure of meloxicam in CYP2C9*3/*3 individuals. *Pharmacogenetics and genomics*, *24*(2), 113-117.
- Zhang, M., Yang, Y., Zhao, G., Di, X., Xu, L., Jiang, N., ... & Xu, X. (2014). Effect of CYP2C9* 3 mutant variants on meloxicam pharmacokinetics in a healthy Chinese population. *Genetics and Molecular Research*, *13*(1), 831-837.

Summary of submission

Bae et al. reported recruiting 1213 male Korean subjects to determine their CYP2C9 genotypes. The authors selected 21 healthy subjects carrying either the *CYP2C9*1/*1* or *CYP2C9*1/*13* genotypes for the study. Pharmacokinetic results revealed that after a single 15 mg oral dose of meloxicam, CYP2C9*13 heterozygotes (i.e., *1/*13) had a 2.42-fold and 1.46-fold increase in AUC $_{0-\infty}$ and $C_{max,}$ respectively, when compared to the wild type genotype (i.e., *1/*1) as summarized in Table 1. In addition, the authors reported subjects with the *1/*13 genotype had a statistically significant increase in the areas under the effect curve from 0 to 72 hours when compared to*1/*1 subjects.

Table 1. Impact of CYP2C9 *13 haplotype on the pharmacokinetics and pharmacodynamics of meloxicam adapted from Bae et al.

PK Parameter	**CYP2C9*1/*1 (n = 12)**	**CYP2C9*1/*13 (n =**
C_{max} (ng/mL)	1558 ± 394	2270 ± 472**
$AUC_{0-\infty}$ (µg.h/mL)	45.2 ± 15.2	109.7 ± 15.8***
$t_{½}$ (h)	21.5 ± 4.6	39.5 ± 5.5***
CL/F (mL/h)	367 ± 117	139 ± 21***
PD Parameter		
Maximum observed TXB_2 inhibition	60.3 ± 117	63.5 ± 21
AUEC (%.h)	2033 ± 631	3337 ± 552***

Each value represents mean ± SD; $AUC_{0-\infty}$, area under the plasma concentration-time curve from time 0 to infinity; $t_{1/2}$, elimination half-life; CL/F, apparent oral clearance; AUEC, area under the effect (percent of inhibition of TXB_2 generation)-time curve, **P<0.01, ***P<0.001 compared with the CYP2C9 *1/*1 group.

In another study, Lee et al. evaluated the impact of CYP2C9*3 haplotype on the pharmacokinetics and pharmacodynamics of meloxicam in 22 male Korean subjects. In this study, after a single 15 mg oral dose of meloxicam, CYP2C9*3 homozygotes (i.e., *3/*3), had an 8.2-fold increase in $AUC_{0-\infty}$ and heterozygous subjects with the *1/*3 genotype had a 1.75-fold increase in $AUC_{0-\infty}$ when compared to subjects with the wildtype genotype (i.e., *1/*1) as shown in Table 2.

Table 2. Pharmacokinetic and pharmacodynamic parameters of meloxicam derived from Lee et al.

Variables	*CYP2C9*1/*1* (*n*=11)	*CYP2C9*1/*3* (*n*=8)	*CYP2C9*3/*3* (*n*=3)	*P* value
Pharmacokinetic parameters				
$t_{1/2}$ (h)	20.9±4.7	35.4±7.5***	123.1±28.4*,#	<0.001
C_{max} (ng/ml)	1535.4±403.9	1614.0±401.3	1993.3±330.1	0.231
AUC_{0-t} (µg h/ml)	37.7±11.7	55.3±10.2*	189.7±16.4***,###	<0.001
$AUC_{0-\infty}$ (µg h/ml)	42.6±14.7	74.6±16.1**	350.2±33.1***,###	<0.001
CL/F (ml/h)	390.5±125.3	211.3±54.9**	43.3±4.0*,#	<0.001
Pharmacodynamic parameters				
Maximum observed TXB_2 inhibition (%)	61.0±8.4	66.0±4.9	83.7±1.6***,##	<0.001
AUEC (% h)	2023±659	2944±429**	10269±588***,###	<0.001

The data are given as arithmetic mean±SD.
AUC_{0-t}, area under the plasma concentration–time curve from time 0 to *t* h (*t*=72 and 144 in the *CYP2C9*1/*1* or *CYP2C9*1/*3* and *CYP2C9*3/*3* individuals, respectively); $AUC_{0-\infty}$, area under the plasma concentration–time curve from time 0 to infinity; AUEC, area under the effect (percent of inhibition of TXB_2 generation)–time curve; CL/F, apparent oral clearance; C_{max}, maximum plasma concentration; $t_{1/2}$, elimination half-life; TXB_2, thromboxane B_2.
*P<0.05; **P<0.01; ***P<0.001 compared with the *CYP2C9*1/*1* group.
#P<0.05; ##P<0.01; ###P<0.001 compared with the *CYP2C9*1/*3* group.

The applicant also refers to a study by Zhang et al. that evaluated the impact of the *3 allele (1075 A>C variant position) on the single and multiple dose pharmacokinetics of meloxicam in 24 healthy male and female volunteers. 7.5 mg meloxicam was administered intramuscularly in a randomly selected single dose group (n=12), while the multiple dose group (n=12) received 15 mg intramuscularly for an unspecified number of times a day for 8 consecutive days. Impact of CYP2C9 *3 haplotype was not evaluated in the single dose cohort as all subjects were of the*1/*1 genotype. The impact of the CYP2C9 *3 haplotype was evaluated in the multiple dose cohort (*1/*1 (n=10); *1/*3 (n=2)). The pharmacokinetic parameters derived are shown as arithmetic mean ± standard deviation in Table 3. No *3/*3 homozygotes were evaluated in this study. The study did not find a statistically significant (p<0.05) difference in C_{max}, AUC_{0-t} or CL/F between

the *1/*1 and the *1/*3 groups after Day 1. After 8 days of meloxicam administration, the authors reported statistically significant ($p<0.05$) increases in the C_{max}, AUC_{0-t}, and CL/F which were 1.71, 2.40, and 2.89-fold higher, respectively, in the *1/*3 group when compared to the *1/*1 group.

Table 3. Impact of CYP2C9 *3 haplotype on the pharmacokinetics of meloxicam derived from Zhang et al.

Parameters	Multi-dose group (day 1)		Multi-dose group (day 8)	
	A/A	A/C	A/A	A/C
AUC (ng.h/ml)	51393.3 ± 646.8	78015.3 ± 950.8	88077.7 ± 19313.2	211146.7 ± 5081.2
Cmax (ng/ml)	2082.5 ± 466.2	1868.5 ± 60.3	2572.8 ± 443.6	4402.8 ± 157.1
CL (L/h)	0.2978 ± 0.0799	0.1565 ± 0.0015	0.1681 ± 0.0471	0.059 ± 0.001

A/A =CYP2C9 *1/*1; A/C =CYP2C9*1/*3

*Reviewer's comment: Bae et al. performed CYP2C9 genotyping for CYP2C9 *2, *3, *4, *5, *11, and *13. The authors reported no subjects with the *2, *4, *5, or *11 were identified in the study, the number of subjects carrying the *3 allele were unspecified. Lee et al. are largely the same authors as Bae et al. In Lee et al, the authors reported performing CYP2C9 genotyping for CYP2C9 *2, *3, and *13 and reported no subjects carrying the *2 allele were identified in the study, however they did not specify if any *13 carriers were identified in the study. Even though Zhang et al. conclude that "significant decreases in meloxicam AUC, C_{max} and CL were noted in heterozygous [CYP2C9*1/*3] variants compared with the wildtype [CYP2C9*1/*1]", the data presented in the study contradicts this conclusion as it demonstrated increases in meloxicam AUC and C_{max} and a decrease in CL/F. Irrespective of the sample sizes in the three studies, the totality of the data in the literature described above, reveal variability in exposure to meloxicam attributable to CYP2C9 genotype. Nonetheless, given the limited data available, there is no compelling evidence from these studies to make specific dosage recommendations based on the observed CYP2C9-genotype-mediated changes in exposure.*

Overview of relevant variant frequencies.
The *CYP2C9* gene is highly polymorphic and the frequency of allelic variants among different ethnic groups vary. For example, the allele frequencies of the common *2 and *3 variants are about 15% and 6%, respectively, in Caucasian populations, and about 3% and 4%, respectively, in Asian populations (PMID: 20504253, 20150829). In contrast, the *5 allele is rarely found in Caucasian and Asian populations, but it is present with a 1.5% frequency in African American populations and Hispanic populations (PMID: 201504253). Other variants that have been described in the promoter and coding regions of *CYP2C9* include the *13 allele, which has been found in Japanese, Korean, and Chinese populations with frequencies of 0.2% to 1% (PMIDs: 19541829, 16187974, 15226678) but has not been observed in African American and Caucasian populations (PMID 20504253). Genotype frequencies of common *CYP2C9* variants across ethnic populations are displayed in figure 1 below.

***CYP2C9* genotype frequencies**

Predicted metabolizer phenotype/genotype	Observed (expected†) frequency (%)				
	African–American‡ (n = 300)	*Asian (n = 102)*	*Caucasian (n = 106)*	*Hispanic (n = 101)*	*Ashkenazi Jewish§ (n = 502)*
Extensive metabolizer					
**1/*1*	75.7 (75.1)	86.3 (84.9)	66.0 (62.1)	70.3 (67.5)	62.4 (62.1)
Intermediate metabolizer					
**1/*2*	4.3 (4.9)	3.9 (5.4)	15.1 (23.8)	9.9 (11.4)	20.7 (20.2)
**1/*3*	3.3 (3.5)	6.9 (7.2)	9.4 (8.9)	8.9 (10.6)	12.0 (13.0)
**1/*5*	2.7 (2.6)	0.0 (0.0)	0.0 (0.0)	2.0 (2.4)	0.2 (0.2)
**1/*6*	1.7 (1.7)	0.0 (0.0)	0.0 (0.0)	1.0 (0.8)	0.0 (0.0)
**1/*8*	8.7 (8.1)	1.0 (1.8)	0.0 (0.0)	1.0 (2.4)	0.0 (0.0)
**1/*11*	2.0 (2.3)	0.0 (0.0)	0.9 (0.7)	1.0 (1.6)	0.0 (0.0)
Total	22.7 (23.1)	11.8 (14.5)	25.5 (33.4)	23.8 (29.3)	32.9 (33.4)
Poor metabolizer					
**2/*2*	0.3 (0.1)	1.0 (0.1)	6.6 (2.3)	1.0 (0.5)	1.2 (1.7)
**2/*3*	0.3 (0.1)	0.0 (0.2)	1.9 (1.7)	1.0 (0.9)	2.6 (2.1)
**2/*8*	0.0 (0.3)	0.0 (0.1)	0.0 (0.0)	1.0 (0.2)	0.0 (0.0)
**3/*3*	0.0 (0.0)	0.0 (0.2)	0.0 (0.3)	1.0 (0.4)	1.0 (0.7)
**3/*5*	0.0 (0.1)	0.0 (0.0)	0.0 (0.0)	1.0 (0.2)	0.0 (0.0)
**3/*8*	0.0 (0.2)	1.0 (0.1)	0.0 (0.0)	0.0 (0.2)	0.0 (0.0)
**3/*11*	0.3 (0.1)	0.0 (0.0)	0.0 (0.1)	0.0 (0.1)	0.0 (0.0)
**5/*6*	0.3 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
**8/*11*	0.3 (0.1)	0.0 (0.0)	0.0 (0.0)	1.0 (0.0)	0.0 (0.0)
Total	1.7 (1.0)	2.0 (0.6)	8.5 (4.4)	6.0 (2.5)	5.0 (4.5)

Extensive metabolizer: CYP2C9*1/*1; *Intermediate metabolizer:* CYP2C9*1/*variant*; *Poor metabolizer:* CYP2C9 *variant/variant*.

n: Number of subjects.

† *Predicted Hardy–Weinberg frequencies*.

‡ *Data from* [18].

Figure 1. Expected and observed CYP2C9 genotype frequencies (PMID: 20504253)

Summary and Conclusions

The proposed labeling change will impact the labeling of other meloxicam products. The proposed language has been modified to 1) provide a general summary of the impact of reduced CYP2C9 activity on meloxicam 2) remove any quantitative information derived from the literature and 3) allude to the frequency of poor metabolizer genotypes across populations.

Recommended language

Section 12.5 Pharmacogenomics
CYP2C9 activity is reduced in individuals with genetic variants such as the CYP2C9*2 and CYP2C9*3 alleles. Limited data from three published reports showed that meloxicam AUC was substantially higher in individuals with reduced CYP2C9 activity, particularly in poor metabolizers (e.g., *3/*3), compared to normal metabolizers (*1/*1). The frequency of CYP2C9 poor metabolizer genotypes varies based on racial/ethnic background but is generally present in <5% of the population.

Section 8 Use in Specific Populations
Poor Metabolizers of CYP2C9 Substrates: In patients who are known or suspected to be poor CYP2C9 metabolizers based on genotype or previous history/experience with other CYP2C9 substrates (such as warfarin and phenytoin) consider dose reduction as they may have abnormally high plasma levels due to reduced metabolic clearance.

4.3 Individual Study Synopses:

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

4.3.1 Study No. 10943701:

2.0 SYNOPSIS

SPONSOR:	Wilmington Pharmaceuticals, LLC 1904 Eastwood Road, Suite 305 Wilmington, NC 28403 United States of America (USA)
NAME OF TEST PRODUCT:	Meloxicam (b) (4) ((b) (4) ODT) Orally Disintegrating 15 mg Tablets Mobic® (meloxicam) 15 mg Tablets (Boehringer Ingelheim)
ACTIVE INGREDIENTS:	Meloxicam
STUDY TITLE:	A Study to Evaluate the Relative Bioavailability of a Meloxicam (b) (4) ((b) (4) ODT) Orally Disintegrating 15 mg Tablet compared to Mobic® (meloxicam) 15 mg Tablets (mfd. by: Boehringer Ingelheim (BI)) in Healthy Volunteers under Fasted Conditions
PRINCIPAL INVESTIGATOR	Soran Hong, MD Novum Pharmaceutical Research Services Wilcrest Green Office Park 3320 Walnut Bend Lane Houston, TX 77042-4712 United States of America (USA)
CLINICAL LABORATORY:	(b) (4)
ANALYTICAL LABORATORY:	

BIOSTATISTICS: [redacted]

STUDY DURATION: The time from first subject dosed to when the last subject completed was approximately 10 days.

STUDY TYPE: A single-dose, randomized, two-treatment, two-period, crossover study under fasted conditions.

OBJECTIVE: The objective of this study was to evaluate the relative bioavailability of a Wilmington Pharmaceuticals LLC's new test formulation of Meloxicam [redacted] ([redacted] ODT) orally disintegrating 15 mg tablet formulation (mfd. by Catalent Pharma Solutions) with that of an already marketed reference, Mobic® (meloxicam) 15 mg tablets (Boehringer Ingelheim (BI)) under fasting conditions in healthy adult volunteers.

METHODOLOGY: This randomized, single-dose, two-treatment, two-period, crossover study was conducted to compare the relative bioavailability of a test formulation of Meloxicam [redacted] ([redacted] ODT) orally disintegrating 15 mg tablet (mfd. by Catalent Pharma Solutions) with that of an already marketed reference, Mobic® (meloxicam) 15 mg tablets (Boehringer Ingelheim (BI)) under fasted conditions. The study was conducted with 32 (32 completing) healthy adult subjects in accordance with 10943701 (Revision 2). In each study period, a single dose (1 x 15 mg meloxicam orally disintegrating tablet or 1 x 15 mg meloxicam tablet) was administered to all subjects following an overnight fast of at least 10 hours. The test formulation was Meloxicam [redacted] ([redacted] ODT) orally disintegrating 15 mg tablet (mfd. by Catalent Pharma Solutions) and the reference formulation was Mobic® (meloxicam) 15 mg tablets (Boehringer Ingelheim (BI)). The subjects received the test product in one study period and the reference product in the other period; the order of administration was according to the dosing randomization schedule. There was a 7-day interval between treatments.

Blood samples were collected pre-dose and at intervals over 72 hours after dosing in each period. The plasma samples from all subjects completing both periods of the study were shipped to the attention of [redacted] for determination of meloxicam concentrations.

Statistical analysis was performed (b) (4) to compare the bioequivalence of the test formulation to the reference product. Bioequivalence was determined based on the confidence intervals for the major pharmacokinetic parameters, AUC0-t, AUC0-inf and Cmax, for meloxicam.

NUMBER OF SUBJECTS: A total of 32 healthy, adult subjects were enrolled and 32 subjects completed the study.

MAIN DIAGNOSIS FOR ENTRY: Diagnosis was not required for this study. All subjects were asymptomatic, healthy adult subjects who met the inclusion/exclusion criteria for this study**.**

TEST PRODUCT: Meloxicam (b) (4) ((b) (4) ODT) 15 mg Orally Disintegrating Tablet
Mfd. by Catalent Pharma Solutions
Batch No: 1024674
Manufacture Date: 17-NOV-2009

REFERENCE PRODUCT: Mobic® (meloxicam) tablets 15 mg
Boehringer Ingelheim (BI)
Lot No: 953687
Expiration Date: NOV 12

ROUTE OF ADMINISTRATION: Oral

DURATION OF TREATMENT: This was a randomized, single-dose, two-treatment, two-period, crossover study. In each study period, a single dose (1 x 15 mg meloxicam orally disintegrating tablet or 1 x 15 mg meloxicam tablet) was administered to all subjects following an overnight fast of at least 10 hours. Subjects received the test product in one study period and the reference product in the other period. The order of treatment administration was according to the dosing randomization schedule. Each dose was separated by a 7-day interval. The study began dosing on 03/02/10 and was completed on 03/12/10.

PRIMARY EFFICACY VARIABLE: Not applicable

SECONDARY EFFICACY VARIABLES: Not applicable

SAFETY ANALYSIS: Adverse events were collected and tabulated. No formal statistical analyses were performed.

STATISTICAL METHODS: Twenty (20) blood samples were collected from each subject; prior to dosing (0, within one hour of dosing), and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4,

5, 6, 7, 8, 10, 12, 16, 24, 36*, 48* and 72* hours post- dose (* returns samples) for analysis of plasma meloxicam concentrations. The analytical data was used to calculate the pharmacokinetic parameters: AUC0-t, AUC0-inf, Cmax, Tmax, Kel and T½. The t in AUC0-t is the time at which the last quantifiable concentration was recorded. The Statistical Analysis System (SAS, Version 9.1.3) was used for all pharmacokinetic and statistical calculations.

Analyses of Variance were performed using the General Linear Model (GLM) procedure of SAS with hypothesis testing for treatment effects at $\alpha = 0.05$. The statistical model contained main effects of sequence, subject within sequence, treatment and period. Sequence effects were tested against the Type III mean square term for subjects within sequence at $\alpha = 0.10$. All other main effects were tested against the mean square error term. Least square means for the treatments (LSMEANS statement), the differences between adjusted treatment means, and the standard errors associated with these differences (ESTIMATE statement) were calculated.

Confidence intervals (90%) for the comparison of test and reference area and peak results were constructed to test the two one-sided hypothesis at the $\alpha = 0.05$ level of significance. The confidence intervals were presented for the ratio of the test-to-reference treatment means and for the geometric mean ratios (obtained from logarithmic transformation).

Determination of bioequivalence was based on the log-transformed data for meloxicam. If the 90% confidence intervals for the major pharmacokinetic parameters, AUC0-t, AUC0-inf, and Cmax, fell within the range of 80.00-125.00% then bioequivalence was demonstrated.

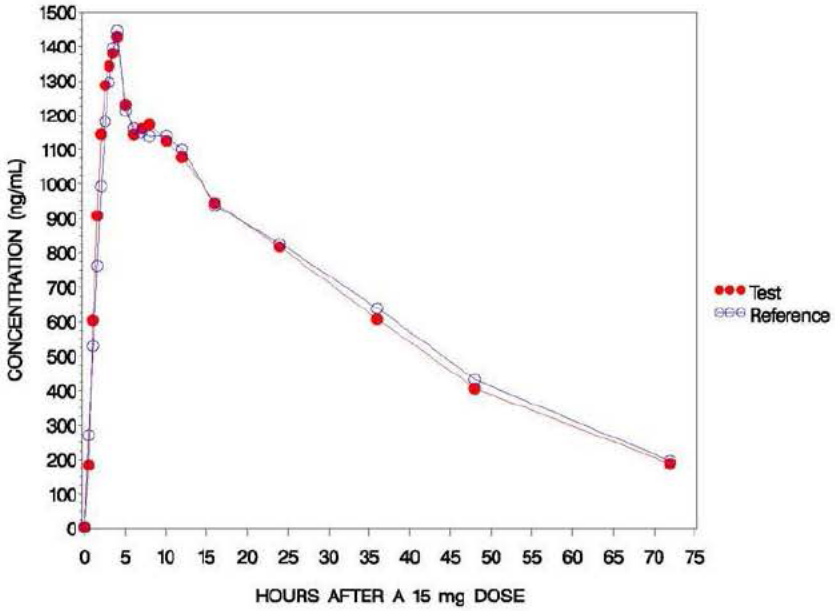
SUMMARY OF RESULTS: Mean concentration versus time plots (linear and ln-linear) are presented below for meloxicam. Tables summarizing the mean test-to-reference ratios and their associated 90% confidence intervals are also provided.

Subject 14 ((b) (6)), Period II (Test A) had pre-dose (0 hour sample) plasma meloxicam levels that were greater than 5% of the measured Cmax value. Therefore, as per FDA Guidelines, all the data for this subject for meloxicam was excluded from the statistical analysis for this study.

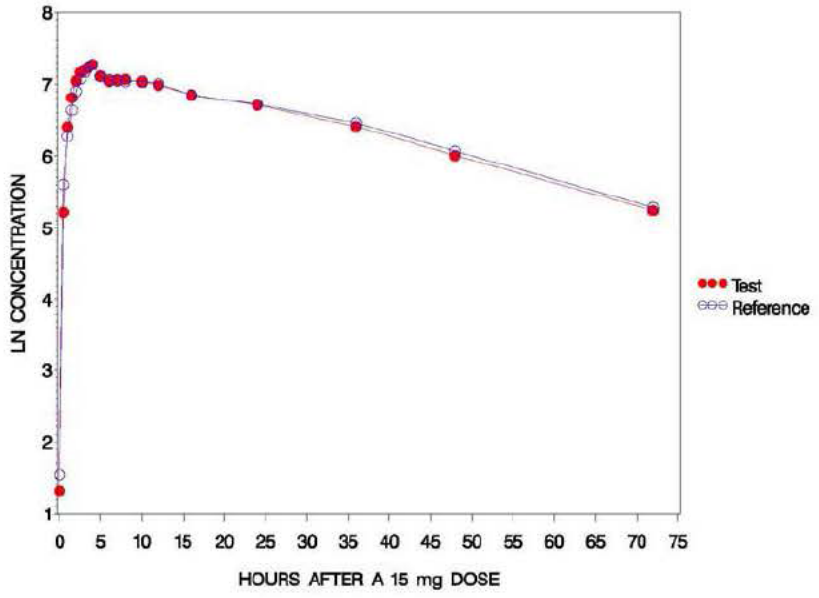
There are 31 sets of data for meloxicam for this study.

Meloxicam

MELOXICAM STUDY NO. 10943701
LEAST-SQUARES MEAN PLASMA CONCENTRATIONS (N=31)



MELOXICAM STUDY NO. 10943701
LEAST-SQUARES MEAN PLASMA CONCENTRATIONS (N=31)



Geometric Means, Ratio of Means, and 90% Confidence Intervals Based on ANOVA of Ln-Transformed Data Analyte: Meloxicam (N = 31)

Parameter	Test A*	Reference B	Ratio	CI**	Intra-Subject %CV
AUC0-t (ng·hr/mL)	44485.24	45227.92	0.9836	0.9546 - 1.0135	6.9449
AUC0-inf (ng·hr/mL)	50001.55	51350.53	0.9737	0.9313 - 1.0181	10.1664
Cmax (ng/mL)	1447.18	1461.99	0.9899	0.9395 - 1.0430	12.1482

*N=30 for AUC0-inf for Test Product A.
**Bioequivalent if confidence intervals are within 0.8000–1.2500 (80.00 to 125.00%).

SAFETY: A total of 6 adverse events (2 Test A, 4 Reference B) were reported by 6 of the 32 subjects who participated in this study. All 6 adverse events were considered "mild" and all 6 resolved spontaneously prior to study completion.. See Appendix 16.2.7 for a listing of adverse events by subject.

CONCLUSION: Based on the statistical analysis of meloxicam, Wilmington Pharmaceuticals, LLC's new formulation of Meloxicam (b) (4) ((b) (4) ODT) orally disintegrating 15 mg tablet (mfd. by Catalent Pharma Solutions) meets the 90% CI for log transformed AUC0-t, AUC0-inf, and Cmax, and therefore has been shown to be bioequivalent to an equal dosage of the reference formulation, Mobic® (meloxicam) 15 mg tablets (Boehringer Ingelheim (BI)) under fasted conditions.

4.3.2 Study No. 10943702:

2.0 SYNOPSIS

SPONSOR:	Wilmington Pharmaceuticals, LLC 1904 Eastwood Road, Suite 305 Wilmington, NC 28403 United States of America (USA)
NAME OF TEST PRODUCT:	Meloxicam [redacted] ([redacted] ODT) Orally Disintegrating 15 mg Tablet
ACTIVE INGREDIENTS:	Meloxicam
STUDY TITLE:	A Study to Evaluate the Effect of Food on the Relative Bioavailability of Meloxicam [redacted] ([redacted] ODT) Orally Disintegrating 15 mg Tablet formulation (mfd. by Catalent Pharma Solutions) in Healthy Volunteers
PRINCIPAL INVESTIGATOR	Soran Hong, MD Novum Pharmaceutical Research Services Wilcrest Green Office Park 3320 Walnut Bend Lane Houston, TX 77042-4712 United States of America (USA)
CLINICAL LABORATORY:	[redacted]
ANALYTICAL LABORATORY:	

BIOSTATISTICS: (b) (4)

STUDY DURATION: The time from first subject dosed to when the last subject completed was approximately 10 days.

STUDY TYPE: A single-dose, randomized, two-treatment, two-period, crossover study under fed and fasting conditions.

OBJECTIVE: The objective of this study was to evaluate the relative bioavailability of Wilmington Pharmaceuticals LLC's new test formulation of Meloxicam (b) (4) ((b) (4) ODT) orally disintegrating 15 mg tablet formulation (mfd. by Catalent Pharma Solutions) when taken following a high fat meal compared to the fasted state in healthy adult volunteers.

METHODOLOGY: This randomized, single-dose, two-treatment, two-period, crossover study was conducted to compare the relative bioavailability of a test formulation of Meloxicam (b) (4) ((b) (4) ODT) orally disintegrating 15 mg tablet (mfd. by Catalent Pharma Solutions) under fed and fasted conditions. The study was conducted with 32 (30 completing) healthy adult subjects in accordance with 10943702 (Revision 2). The test formulation, Meloxicam (b) (4) ((b) (4) ODT) orally disintegrating 15 mg tablet (mfd. by Catalent Pharma Solutions), was administered to all subjects in each period of the study. In each study period, a single dose (1 x 15 mg meloxicam orally disintegrating tablet) was administered to designated subjects following an overnight fast of at least 10 hours or following a standardized high fat breakfast preceded by an overnight fast of at least 10 hours. The order of administration was according to the dosing randomization schedule. There was a 7-day interval between treatments.

Blood samples were collected pre-dose and at intervals over 72 hours after dosing in each period. The plasma samples from all subjects completing both periods of the study were shipped to the attention of (b) (4) for determination of meloxicam concentrations.

Statistical analysis was performed (b) (4) to evaluate the relative bioavailability of the test formulation under fed and fasted conditions.

NUMBER OF SUBJECTS: A total of 32 healthy, adult subjects were enrolled and 30 subjects completed the study.

MAIN DIAGNOSIS FOR ENTRY: Diagnosis was not required for this study. All subjects were asymptomatic, healthy adult subjects who met the inclusion/exclusion criteria for this study**.**

TEST A: Meloxicam (b) (4) ((b) (4) ODT) 15 mg Orally Disintegrating Tablet
Mfd. by Catalent Pharma Solutions
Batch No: 1024674
Manufacture Date: 17-NOV-2009
Following a high fat standardized breakfast

REFERENCE B: Meloxicam (b) (4) ((b) (4) ODT) 15 mg Orally Disintegrating Tablet
Mfd. by Catalent Pharma Solutions
Batch No: 1024674
Manufacture Date: 17-NOV-2009
Following an overnight fast.

ROUTE OF ADMINISTRATION: Oral

DURATION OF TREATMENT: This was a randomized, single-dose, two-treatment, two-period, crossover study. The test formulation, Meloxicam (b) (4) ((b) (4) ODT) orally disintegrating 15 mg tablet (mfd. by Catalent Pharma Solutions), was administered to all subjects in each period of the study. In each study period, a single dose (1 x 15 mg meloxicam orally disintegrating tablet) was administered to designated subjects following an overnight fast of at least 10 hours or following a standardized high fat breakfast preceded by an overnight fast of at least 10 hours. The order of treatment administration was according to the dosing randomization schedule. Each dose was separated by a 7-day interval. The study began dosing on 03/06/10 and was completed on 03/16/10.

PRIMARY EFFICACY VARIABLE: Not applicable.

SECONDARY EFFICACY VARIABLES: Not applicable.

SAFETY ANALYSIS: Adverse events were collected and tabulated. No formal statistical analyses were performed.

STATISTICAL METHODS: Twenty (20) blood samples were collected from each subject: prior to dosing (0, within 90 minutes of dosing and prior to breakfast), and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 16, 24, 36*, 48* and 72* hours post- dose (*

return samples) for analysis of plasma meloxicam concentrations. The analytical data was used to calculate the pharmacokinetic parameters: AUC0-t, AUC0-inf, Cmax, Tmax, Kel and T½. The t in AUC0-t is the time at which the last quantifiable concentration was recorded. The Statistical Analysis System (SAS, Version 9.1.3) was used for all pharmacokinetic and statistical calculations.

Analyses of Variance were performed using the General Linear Model (GLM) procedure of SAS with hypothesis testing for treatment effects at $\alpha = 0.05$. The statistical model contained main effects of sequence, subject within sequence, treatment and period. Sequence effects were tested against the Type III mean square term for subjects within sequence at $\alpha = 0.10$. All other main effects were tested against the mean square error term. Least square means for the treatments (LSMEANS statement), the differences between adjusted treatment means, and the standard errors associated with these differences (ESTIMATE statement) were calculated.

Confidence intervals (90%) for the comparison of test and reference area and peak results were constructed to test the two one-sided hypothesis at the $\alpha = 0.05$ level of significance. The confidence intervals are presented for the geometric mean ratios (obtained from logarithmic transformed data).

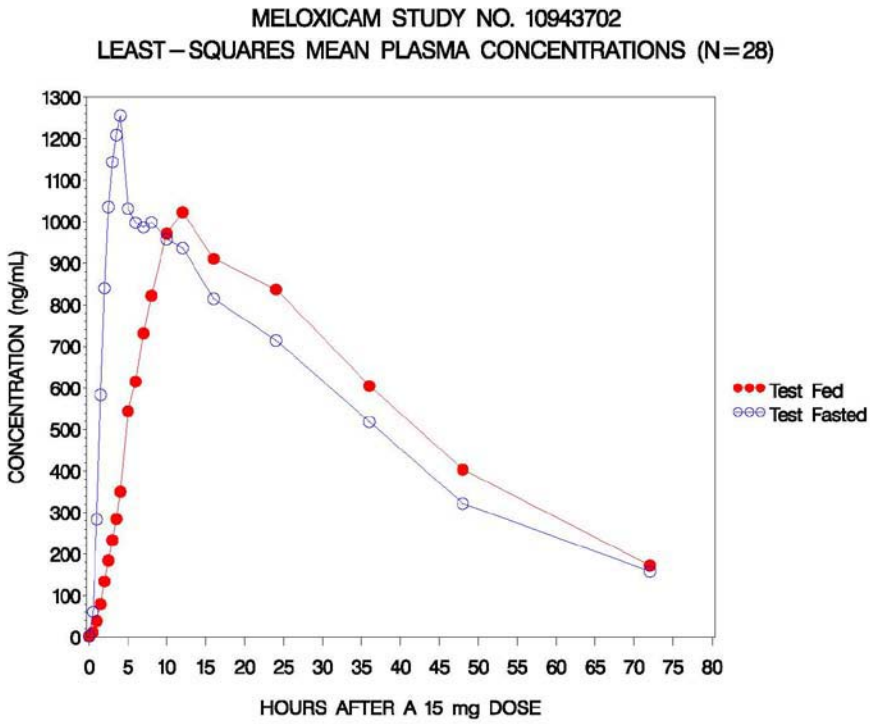
If the 90% confidence intervals for the AUCt, AUCinf, and Cmax pharmacokinetic parameters, fell within the range of 80.00-125.00%, then it was determined that food had no effect on the bioavailability of Wilmington Pharmaceuticals, LLC's Meloxicam (b) (4) ((b) (4) ODT) orally disintegrating 15 mg tablet (mfd. by Catalent Pharma Solutions). If the 90% CI did not fall within the range 80.00-125%, then the effect of food on the bioavailability of meloxicam was described. Tmax and Tlag under fasted and fed conditions were compared and the clinical relevance of any significant differences was considered.

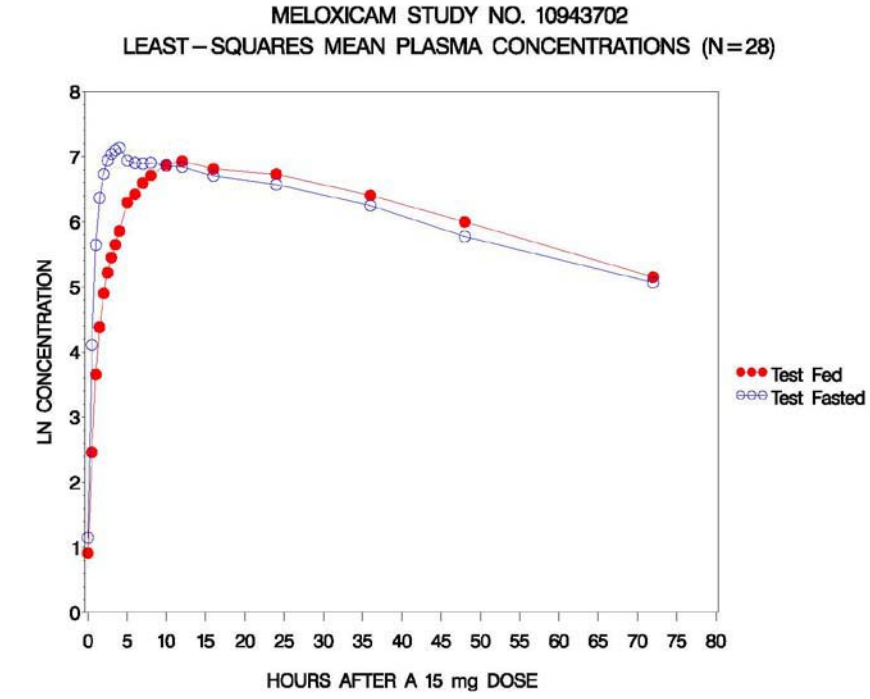
SUMMARY OF RESULTS: Mean concentration versus time plots (linear and ln-linear) are presented below for meloxicam. Tables summarizing the mean test-to-reference ratios and their associated 90% confidence intervals are also provided.

Subject 27 ((b) (6)), Period II (Test A) and Subject 30 ((b) (6)), Period II (Test A), had pre-dose (0 hour sample) plasma meloxicam levels that were greater than 5% of the measured Cmax value. Therefore, as per FDA Guidelines, all the data for these subjects for meloxicam was excluded from the statistical analysis for this study.

There are 28 sets of data for meloxicam for this study.

Meloxicam





Geometric Means, Ratio of Means, and 90% Confidence Intervals Based on ANOVA of Ln-Transformed Data Analyte: Meloxicam (N = 28)

Parameter	Test A*	Reference B	Ratio	CI	Intra-Subject %CV
AUC0-t (ng·hr/mL)	38239.78	36747.75	1.0406	0.9538 - 1.1353	19.0832
AUC0-inf (ng·hr/mL)	41758.70	42081.41	0.9923	0.9558 - 1.0302	7.9345
Cmax (ng/mL)	1150.88	1227.26	0.9378	0.8585 - 1.0244	19.3520

*N=27 for AUC0-inf for Test Product A.

SAFETY: A total of 10 adverse events (7 Test A, 3 Reference B) were reported by 7 of the 32 subjects who participated in this study. All 10 adverse events were considered "mild"; 8 resolved spontaneously prior to study completion, one (1) resolved with treatment, and one (1) had not resolved by the end of the study. See Appendix 16.2.7 for a listing of adverse events by subject.

CONCLUSION: Dosing of Wilmington Pharmaceuticals, LLC's new formulation of Meloxicam (b) (4) ((b) (4) ODT) orally disintegrating 15 mg tablet (mfd. by Catalent Pharma Solutions) following a high fat breakfast compared to when dosed under fasted conditions had no effect on the bioavailability of meloxicam, meeting the 90% CI for the log transformed AUC0-t, AUC0-inf and Cmax.

Food did have a statistically significant (Wilcoxon Signed Rank, p value < 0.0001) effect on the time course of absorption as the median Tmax was 12.0 hours for the test formulation under fed conditions as compared to a median Tmax of 4.0 when given in the fasted state. The possible clinical significance of this delay in Tmax is unknown.

Although food also had a statistically significant (Wilcoxon Signed Rank, p value < 0.0039) effect on the time at which the first reportable plasma meloxicam concentration (Tlag) was reported (40 minutes in the fed state compared to 30 minutes in the fasted state) this is not considered to have any clinical significance.

The formulation was well tolerated under fed and fasted conditions.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DEEP KWATRA
09/17/2018

OLUSEYI A ADENIYI
09/17/2018

CHRISTIAN GRIMSTEIN
09/17/2018

YUN XU
09/17/2018

M E M O R A N D U M

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

DATE: 3/19/2018

TO: Division of Anesthesia Analgesia and Addiction Products
Office of Drug Evaluation II

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 211210

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the sites listed below. The inspectional outcome from the inspections was classified as No Action Indicated (NAI).

Inspection Sites

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	
Clinical	Novum Pharmaceutical Research Services	3320 Walnut Bend Lane, Houston, TX

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

/s/

SHILA S NKAH
03/19/2018