

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207233Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

NDA:	207233
Submission Date:	December 23 rd 2014
Relevant IND(s):	114045
Submission Type; Code:	505 (b) (2)
Reference Drug:	Mobic (NDA020938)
Brand Name:	VIVLODEX capsules
Generic Name:	Meloxicam
Formulation; Strength(s):	Immediate-release capsules; 5 mg and 10 mg
Clinical Pharmacology Reviewer:	Deep Kwatra, Ph.D.
Team Leader:	Yun, Xu, Ph.D.
OCP Division:	Division of Clinical Pharmacology II
OND Division:	Anesthesia Analgesia and Addiction Products
Sponsor:	Iroko Pharmaceuticals, LLC
Proposed Indication:	(b) (4) management of OA pain
Proposed Dosage Regimen:	5 mg or 10 mg orally once daily.

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1.0 Executive Summary

1.1 Recommendation

From the Clinical Pharmacology perspective, NDA 207233 submitted on 12/23/2014 is acceptable.

1.2 Phase 4 Commitments

None

1.3. Summary of Clinical Pharmacology Findings

Iroko Pharmaceuticals, LLC submitted a 505 (b) (2) application for VIVLODEX capsules, an immediate-release (IR) formulation of meloxicam for the (b) (4) pain in adults. The applicant conducted a Pivotal Phase 3 safety and efficacy placebo controlled trial (MEL3-12-02) and using the to-be-marketed (TBM) formulation, in conjunction with the Agency's previous findings of safety and efficacy for the reference drug Mobic (NDA-020938). As a 505(b)(2) NDA, for establishing the clinical bridge, Iroko conducted a comparative bioavailability (BA), dose proportionality and food effect trial with TBM formulation (MEL1-12-04) against Mobic 15 mg IR tablets of NDA-020938 (Boehringer Ingelheim Pharmaceuticals Inc).

The dose strengths for VIVLODEX oral capsules are 5 and 10 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. The proposed VIVLOEX capsules are a reformulation of meloxicam with reduced particle size made by the sponsor's trademarked SoluMatrix™ technology. The VIVLODEX capsules contain 5 mg or 10 mg of meloxicam as the sole analgesic ingredient, representing a 33% lower meloxicam dose compared to reference Mobic (7.5 mg and 15 mg).

The 33% lower dose calculation of 5 mg and 10 mg VIVLODEX capsules was made based on meloxicam free-drug (7.5 and 15 mg Mobic capsules contain 7.5 and 15 mg of meloxicam and other excipients, respectively).

Sponsor's rationale of reduced particle size is to increase the surface area to-mass ratio and thereby facilitate the rapid absorption in the GI tract. This Sponsor has an approval for Zorvolex capsules (Diclofenac) and TIVORBEX (Indomethacin) with the similar rationale. With regard to improving of absorption / bioavailability of the proposed product; for reference drug Mobic immediate release tablets, the peak concentrations (C_{max}) of meloxicam appear at 5 hours (T_{max}) and the bioavailability (BA) of meloxicam after oral administration is almost 89%. Therefore, there may be little room for a new formulation to improve on the extent of absorption in terms of bioavailability of the drug, but there is potential to improve the rate of absorption to reduce the T_{max}.

For this NDA, the safety, the end of Phase 2 were held on 01/18/2012, 11/13/2012 respectively under IND 114045. The clinical development program includes one clinical pharmacology study with TBM formulation (reviewed) and two clinical pharmacology studies with pilot formulation (not reviewed), one phase 3 safety clinical study and one pivotal phase 3 safety and efficacy study using the TBM formulation.

Clinical Pharmacology Studies:

Three clinical pharmacology studies, MEL1-11-01, population-PK and MEL1-12-04 were conducted for this application. Out of these three studies, MEL1-11-01 and population-PK studies were conducted with initial proof of concept formulations for the sponsor's internal decision making and hence not reviewed. The study MEL1-12-04 was conducted with commercial scale formulation that fulfills the clinical pharmacology information of the proposed product from regulatory requirement perspective.

Phase 1 Study MELI-12-04 (with commercial scale formulation):

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

Clinical Studies:

Sponsor conducted two Phase 3 clinical studies. The two Phase 3 studies, MEL3-12-02 and MEL3-12-03 were conducted with commercial scale formulation serve for assessing the clinical safety and efficacy for this product.

Phase 3 Studies (with commercial scale formulation):

- **MEL3-12-02** (Pivotal Phase 3 Efficacy and Safety study): Multicenter, Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Fixed-Dose, Parallel-Group, Efficacy, and Safety Study of Meloxicam SoluMatrix™ Capsules in Patients with Pain Due to Osteoarthritis of the Knee or Hip.
- **MEL3-12-03** (Phase 3 Safety study): A Multicenter, Open-Label, Safety Study of Meloxicam SoluMatrix™ Capsules in Subjects with Osteoarthritis of the Knee or Hip

Relative bioavailability of VIVLODEX capsules compared to reference meloxicam tablets (MELI-12-04):

The relative BA of VIVLODEX 10 mg capsules was compared to meloxicam 15 mg capsules as a part of the study MELI-12-04, under fasting conditions in 27 healthy subjects.

- VIVLODEX 10 mg dose not result in similar systemic exposure as reference meloxicam 15 mg tablets and are not bioequivalent.
- When taken under fasted conditions, 33% lower dose of VIVLODEX capsules (10 mg) compared to meloxicam tablets (15 mg) results in equivalent (geometric mean) peak concentrations (C_{max}), and 18 and 33 % lower (geometric mean) AUC_{0-t} and AUC_{0-∞}, respectively. Since the 33% lower dose of VIVLODEX results in 33% lower AUC_{0-∞} compared to Mobic, the new formulation does not improved the bioavailability of meloxicam. The median time to reach peak concentrations (T_{max}) for VIVLODEX capsules is two hours earlier compared to meloxicam tablets (VIVLODEX 2 hours versus Mobic 4 hours).

- There were no significant differences in elimination half-life ($t_{1/2}$) between VIVLODEX capsules and Mobic tablets (VIVLODEX 22.04 hours vs. Mobic tablets 23.64 hours).

Dose Proportionality between 5 and 10 VIVLODEX capsules:

- The two strengths VIVLODEX 5 and 10 mg capsules are compositionally proportional. The 5 and 10 mg strengths show dose proportional pharmacokinetics for C_{max} and AUC under fasted conditions.

Food Effect on VIVLODEX and mobic tablets:

The food effect was assessed for VIVLODEX 10 mg capsules in 27 (Fasted) and 26 (Fed) healthy subjects, respectively.

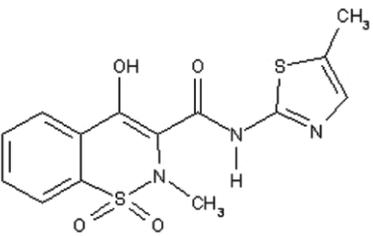
- When taken under fed conditions, VIVLODEX capsules results in decreasing rate (C_{max} and T_{max}) but not the overall extent of meloxicam absorption (AUC_{0-∞}).
 - Under fed conditions, VIVLODEX 10 mg capsules results in 22% lower C_{max}, 6% lower AUC_{0-t} and 8% lower AUC_{0-∞} respectively compared to the fasted conditions. Taking VIVLODEX with food delayed the T_{max} by 3 hours (2 hours fasted vs. 5.00 hours fed).
- Under fed conditions, the reference Mobic tablet results in 22% higher C_{max} and no change in AUC compared to fasted conditions. Taking Mobic tablets with food resulted in T_{max} achieved between 5 and 6 hours. The source of reference food effect data is from the label of the reference drug.
- The Mobic label states that can be administered without regard to timing of meals. The observed food effect for VIVLODEX capsules though not comparable to the reference meloxicam tablets, significant changes were not observed in the overall exposure and hence it can be labeled to be taken without regard to timing of meal.

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

2.0 Question Based Review

2.1 General Attributes of the Drug

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

Drug Name	Meloxicam
Chemical Name	4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide
Structure	 The chemical structure of Meloxicam is shown. It consists of a benzothiazine ring system with a sulfonamide group at position 3, a methyl group on the nitrogen at position 2, and a 4-hydroxy-5-methylthiazol-2-yl group attached to the benzothiazine ring at position 4. The sulfonamide group is shown as a sulfur atom double-bonded to two oxygen atoms and single-bonded to a nitrogen atom which is also bonded to a methyl group.
Molecular Formula	C ₁₄ H ₁₃ N ₃ O ₄ S ₂
Molecular Weight	351.4

Formulation:

VIVLODEX capsules are a reformulation of meloxicam with reduced particle size. VIVLODEX capsules are 33% lower in meloxicam dose compared to Mobic capsules. The two strengths of VIVLODEX capsules are 5 mg and 10 mg compared 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
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 VIVLODEX capsules?

The proposed commercial dosage forms of VIVLODEX capsules include 5 mg and 10 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 VIVLODEX capsules 20 and 40 mg strengths

Component	Quality Standard	Function	Strength	
			5	10
			Amount per Capsule (mg/capsule weight)	Amount per Capsule (mg/capsule weight)
Meloxicam	USP	Active pharmaceutical ingredient	5	10
Lactose monohydrate	NF	(b) (4)	(b) (4)	(b) (4)
Sodium lauryl sulfate	NF	(b) (4)	(b) (4)	(b) (4)
Microcrystalline cellulose	NF	(b) (4)	(b) (4)	(b) (4)
Croscarmellose sodium	NF	(b) (4)	(b) (4)	(b) (4)

Sodium stearyl fumarate	NF	(b) (4)	(b) (4)	(b) (4)
Total capsule fill weight	-		125	250

NF - National Formulary, 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 VIVLODEX capsules is the management of OA pain.

2.1.5 What are the proposed dosage and route of administration?

VIVLODEX capsules are intended for oral administration. The proposed dosage is 5 mg or 10 mg once daily.

2.1.6 What is the core studies submitted in this NDA?

The core clinical development program includes one clinical pharmacology study, one clinical safety and efficacy study and one Phase 3 safety study using the final to-be marketed formulation.

- **MEL1-12-04:** A Phase 1, randomized, 4-period, 4-treatment, 4-sequence, single-dose, crossover pharmacokinetic (PK) trial evaluated the pharmacokinetic properties of Vivlodex Capsules 5 mg and 10 mg (Commercial Formulation) and Mobic 15 mg tablets in healthy subjects under fed and fasted conditions.
- **MEL3-12-02:** A Phase 3, multicenter, randomized, double-blind, double-dummy, placebo-controlled, fixed-dose, parallel-group trial evaluated the efficacy and safety of Vivlodex Capsules 5 mg and 10 mg (Commercial Formulation) in subjects with pain due to OA of the knee or hip.
- **MEL3-12-03:** A Phase 3, multicenter, open-label trial evaluated the safety and tolerability of Vivlodex Capsules 10 mg (Commercial Formulation) in subjects with pain due to OA of the knee or hip.

2.2 General Clinical Pharmacology

The clinical efficacy studies, MEL3-12-02 and MEL3-12-03 for (b) (4) of pain due to OA of the knee or hip and the MEL1-12-04 clinical pharmacology study characterizing the formulation form the basis to support the dosing for this NDA

For final assessment of the safety and efficacy findings, see Clinical review by Dr. Mary A. Luckett (Clinical Reviewer).

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

No biological biomarker was assessed in this NDA. In two placebo-controlled studies the primary endpoint was mean change in the WOMAC pain subscale score from Visit 2 (Baseline) to Visit 5 (Week 12).

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. VIVLODEX 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 VIVLODEX 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 similarly demonstrated for the Vivlodex Capsules 5 mg and 10 mg doses (MEL1-12-04) in Vivlodex Capsules clinical trial.

Dose-proportionality of VIVLODEX Capsules:

The dose proportionality between two strengths, 5 and 10 mg VIVLODEX capsules was assessed as part of study MEL1-12-04 under fasted conditions. Note that the two strengths VIVLODEX, 5 and 10 mg were compositionally proportional.

Treatments:

- VIVLODEX capsules 5 mg Fasted (Batch # L0309610)
- VIVLODEX capsules 10 mg Fasted (Batch # L0309611)

The mean \pm SD concentration-time profiles and PK parameters for 5 and 10 mg VIVLODEX capsules are shown in the Figures 2.2.5 and Table 2.2.5a, respectively. The dose proportionality for dose normalized meloxicam plasma PK parameters (5 mg vs. 10 mg) is shown in the Table 2.2.5b. The dose normalized PK parameters show that 5 and 10 mg VIVLODEX capsules results in dose proportional pharmacokinetics for C_{max} and AUC under fasted conditions

Figure 2.2.5. Mean dose-normalized plasma concentration-time profiles after single dose administration of VIVLODEX 5 and 10 mg under fasted conditions.

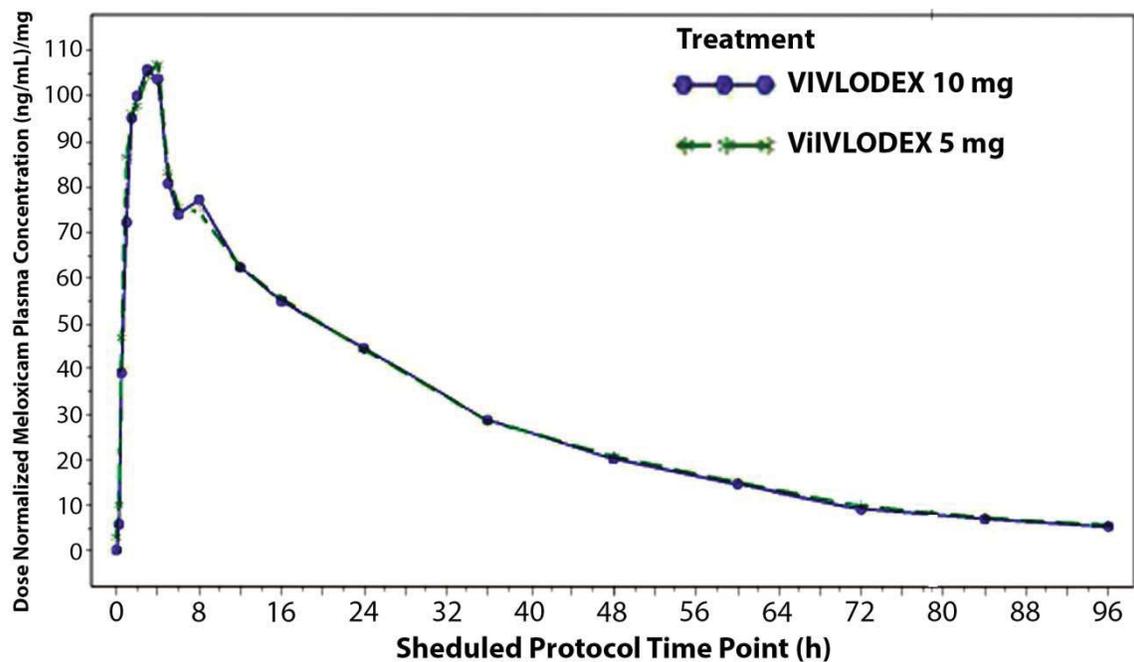


Table 2.2.5a: PK parameters for VIVLODEX 5 and 10 mg dose strengths under fasted conditions.

Parameter	VIVLODEX® 10 mg Geometric LS mean	Geometric LS Means 95% CI	VIVLODEX® 5 mg Geometric LS mean	Geometric LS Means 95% CI
C _{max} (ng/mL)	1230.62	(1129.67, 1340.60)	626.74	(574.93, 683.22)
AUC _{0-t} (hr*ng/mL)	27213.63	(24285.61, 30494.66)	13672.43	(12196.44, 15327.05)
AUC _{0-∞} (hr*ng/mL)	27857.69	(24918.55, 31143.49)	13913.03	(12430.29, 15572.63)

Table 2.2.5b: Dose proportionality for dose normalized meloxicam plasma PK parameters for 10 mg versus 5 mg.

Parameter	Geometric LS mean ratio (10 mg / 5 mg)	90% CI of ratio
C _{max} (ng/mL)	0.982	0.935, 1.031
AUC _{0-t} (hr*ng/mL)	0.995	0.955, 1.037
AUC _{0-∞} (hr*ng/mL)	1.001	0.954, 1.050

2.3. Intrinsic factors

2.3.1. What is the pediatric plan?

Pediatric Study Plan (PSP) for VIVLODEX for (b) (4) 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” in the proposed indication.

Reviewer comments:

The initial PSP for VIVLODEX 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 VIVLODEX® capsules compared to the reference drug, Meloxicam Tablet?

The relative bioavailability of VIVLODEX® 10 mg capsules was compared to reference Meloxicam 15 mg Tablets (Mobic) under fasted conditions as a part of study MEL1-12-04. This study was done using commercial scale formulation of VIVLODEX. A total number of 27 healthy subjects completed the treatments.

Treatments:

- Test VIVLODEX capsules 5 mg (Batch # L0309610) Fasted
- Test VIVLODEX capsules 10 mg (Batch # L0309611) Fasted
- Test VIVLODEX capsules 10 mg (Batch # L0309611) Fed
- Reference Mobic tablets 15 mg Fasted

There was at least a 14-day washout interval between doses. Blood samples for PK were collected for 96 hours after dosing.

Results:

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

- VIVLODEX 10 mg capsules does not result in similar systemic exposure as reference meloxicam 15 mg IR capsules and are not bioequivalent.
- When taken under fasted conditions, 33% lower dose of VIVLODEX capsules (10 mg) compared to mobic tablets (15 mg) results equivalent peak concentrations

(Cmax) and 18 and 33 % lower (geometric mean) AUC_{0-t} and AUC_{0-∞}, respectively. The median time to reach peak concentrations (Tmax) for VIVLODEX capsules is 2 hours earlier compared to Meloxicam tablets (VIVLODEX 2 hours versus mobic tablets 4 hours).

- There were no differences in elimination half-life (t_{1/2}) between VIVLODEX capsules and mobic tablets (VIVLODEX 22.04 hours vs. mobic tablets 23.64 hours).

Figure 2.4.1a: Mean meloxicam plasma concentration-time profiles after administration of VIVLODEX capsules (5mg & 10 mg) and mobic tablet (15mg) under fasted conditions.

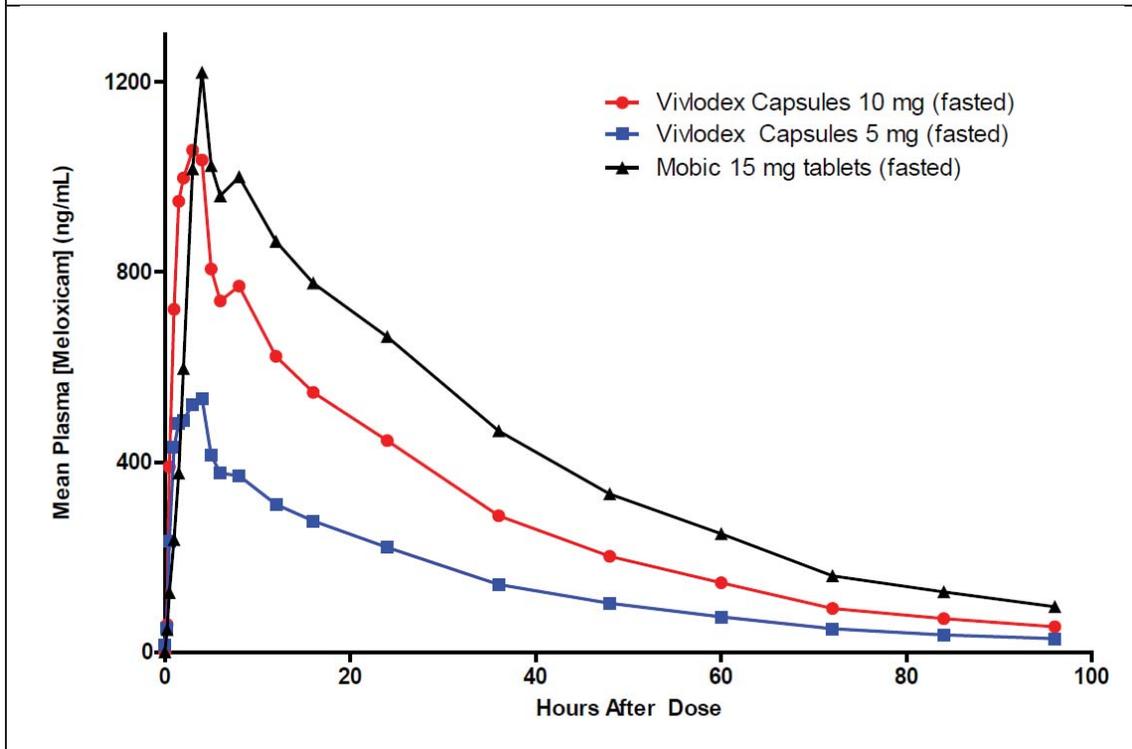


Table 2.4.1a. Pharmacokinetic parameters comparing VIVLODEX capsules and mobic tablets under fasted conditions.

Parameter Arithmetic mean ± SD (n)	VIVLODEX capsules Fasted		Mobic tablets (15 mg) Fasted (27)
	5 mg (26)	10 mg (27)	
Cmax (ng/mL)	642.4±138.5	1252.8±254.2	1288.8±424.4
AUC _{0-t} (hr*ng/mL)	14206.5±5415.3	28190.5±9264.7	39093.8±16500.2
AUC _{0-∞} (hr*ng/mL)	13610.5±3342.7	29173.0±11042.1	40875.6±11733.5
Tmax (hr)*	2.00 (0.50, 4.07)	2.00 (1.00, 5.00)	4.00 (2.02, 8.00)
T _{1/2} (hr)	22.32±10.91	22.04±10.08	23.64±10.04

*Median (min, max);

Table 2.4.1b: Geometric LS mean ratios and 90% confidence intervals for Cmax AUC_{0-t} and AUC_{0-∞} of VIVLODEX (10 mg) versus mobic tablets (15 mg) in fasted conditions.

Parameter	Geometric LS mean (Geometric LS Mean 95%, CI)		Geometric LS mean ratio (90% CI of ratio) [VIVLODEX 10 mg / Mobic 15 mg]
	VIVLODEX (10 mg)	Mobic (15 mg)	
Cmax (ng/mL)	1225.36 (1043.79, 1438.51)	1135.03 (966.79, 1332.54)	1.080 (0.905, 1.288)
AUC _{0-t} (ng.h/mL)	26971.67 (22146.05, 32848.79)	32793.86 (26921.01, 39947.88)	0.822 (0.676, 1.001)
AUC _{0-∞} (ng h/mL)	28041.55 (25081.98, 31350.35)	41616.78 (37166.78, 46599.59)	0.674 (0.641, 0.708)

2.4.2 What is the effect of food on the BA of VIVLODEX in comparison to the mobic tablets?

The food effect was assessed for VIVLODEX 10 mg capsules in 27 (Fasted) and 26 (Fed) healthy subjects, respectively.

There was at least a 14-day washout interval between doses. Blood samples for PK were collected for 96 hours after dosing.

Results:

The Figure 2.4.2 shows the plasma concentration-time profiles of VIVLODEX 10 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-∞} and Cmax 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, VIVLODEX capsules results in decreased the rate (Cmax and Tmax) but not the overall extent of meloxicam absorption (AUC_{0-∞}).
- Under fed conditions, VIVLODEX 10 mg capsules results in 22% lower Cmax, 6% lower AUC_{0-t} and 8% lower AUC_{0-∞} respectively compared to the fasted conditions. Taking VIVLODEX with food delayed the Tmax by 3 hours (2 hours fasted vs. 5.00 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.

Figure 2.4.2a: Mean meloxicam plasma conc.-time profiles for 10 mg VIVLODEX capsules under fasted and fed conditions (Study MEL1-12-04)

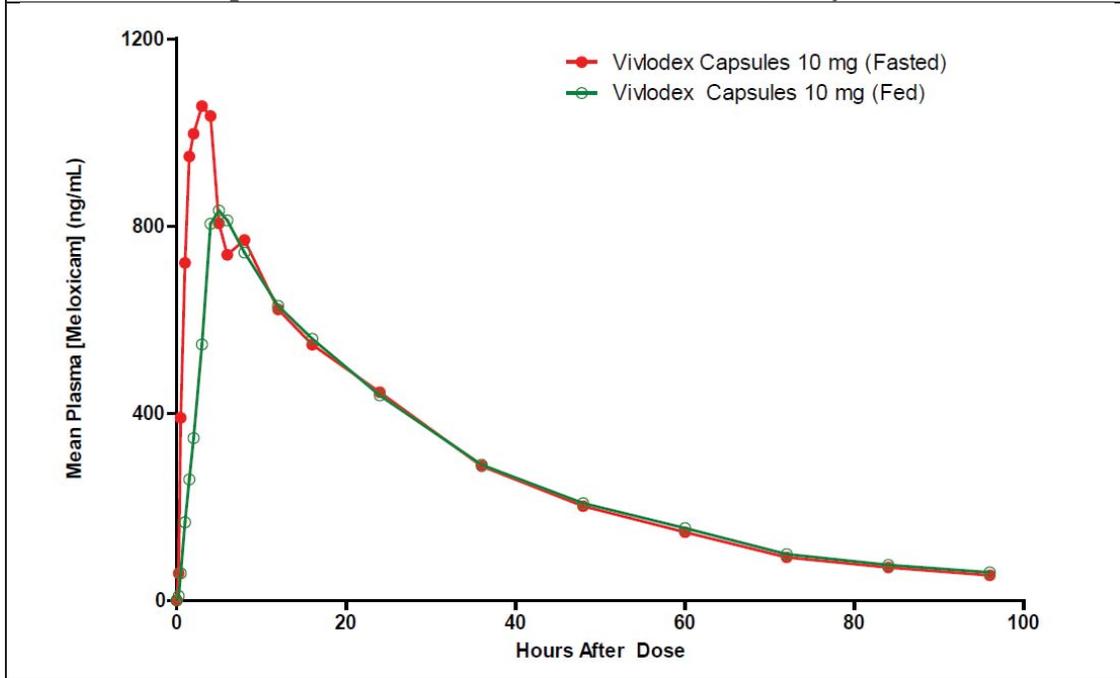


Table 2.4.2a. Pharmacokinetic parameters of meloxicam after administration of VIVLODEX capsules under fasted and fed conditions

Parameter	VIVLODEX Geometric LS Mean (Geometric LS Mean 95% CI) (Study MEL1-12-04)	
	Fasted	Fed
	Cmax (ng/mL)	1255.36 (1043.79, 1438.51)
AUC _{0-t} (hr*ng/mL)	26971.67 (22146.05, 32848.79)	25249.69 (20661.53, 30856.71)
AUC _{0-∞} (hr*ng/mL)	28041.55 (25081.98, 31350.35)	25644.63 (22919.15, 28694.22)
Tmax (hr)	2.22 (1.85 – 2.66)	5.18 (4.31 – 6.24)

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

PK parameter	Treatment Ratio (90% CI of ratio)
	VIVLODEX Fasted / VIVLODEX Fed
Cmax	0.783 (0.655, 0.936)
AUC _{0-t}	0.936 (0.767, 1.142)
AUC _{0-∞}	0.915 (0.870, 0.961)
Tmax (hr)*	3.00 (2.02, 4.01)

* Hodges-Lehman Estimate of Median Difference (90% CI for estimate of Median Difference)

Reviewer comments:

The Mobic label states that it can be administered without regard to timing of meals. The observed food effect for VIVLODEX capsules though not comparable to the reference meloxicam tablets, significant changes were not observed in the overall exposure and hence it can be labeled to be taken without regard to timing of meal.

2.5. Analytical Section

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

Clinical Facility:

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

- Clinical study MEL1-12-04 study duration was between 05 September 2012 to 20 November 2012

Bio-analytical Facility:

(b) (4)

Assay of samples were conducted from 30 Jul 2013 (receipt of first samples) to 21 Aug 2013 (date of last injection)

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

Bio-analytical Validation:

Study Number:	QPS 42-1358
Analyte Name:	Meloxicam
Internal Standard (IS):	¹³ C, ₃ Meloxicam
Analytical Method Type:	LC-MS/MS
Extraction Method:	Protein Precipitation
Sample Volume:	50 L
QC Concentrations:	10, 30, 250, 2250, and 4000 ng/mL
Standard Curve Concentrations:	10, 20, 50, 150, 500, 1500, 4500, and 5000 ng/mL
Lower Limit of Quantitation:	10 ng/mL
Upper Limit of Quantitation:	5000 ng/mL
Average Recovery of Analyte (%):	110.4
Average Recovery of Internal Standard (%):	Not applicable since a stable isotope

labeled internal standard was used.

LLOQ QC Intraday Precision Range (%CV):	2.4 to 5.5
LLOQ QC Intraday Accuracy Range (%RE):	-7.8 to 2.0
Analytical QC Intraday Precision Range (%CV):	0.7 to 2.1
Analytical QC Intraday Accuracy Range (%RE):	0.3 to 10.0
LLOQ QC Interday Precision (%CV):	6.1
LLOQ QC Interday Accuracy (%RE):	-1.9
Analytical QC Interday Precision Range (%CV):	1.2 to 2.2
Analytical QC Interday Accuracy Range (%RE):	0.5 to 8.0
Stock Solution Stability in DMSO:	91 Days at -20°C 7 Hours at Room Temperature
Spiking Solution Stability in DMSO:	86 Days at 4°C 7 Hours at Room Temperature
Processed Sample Stability:	143 Hours at 4°C
Benchtop Stability in Plasma:	21 Hours at Room Temperature
Freeze/Thaw Stability in Plasma:	5 Cycles at -20°C and -70°C
Benchtop Stability in Whole Blood:	2 Hours at Room Temperature
Long-term Storage Stability in Plasma:	98 Days at -20°C and -70°C
Dilution Integrity:	25000 ng/mL diluted 10-fold
Selectivity:	20% LLOQ for analyte; 5.0% for IS

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.

Reviewer Comments:

This labeling recommendation for hepatic impairment for VIVLODEX is updated in comparison to previous Meloxicam products. The updated sections are in (b) (4) 12.3. These recommendations are due to new requirements based on the SEALD LABELING high level comments.

2.2 Non-Interchangeability with Other Formulations of Meloxicam

VIVLODEX capsules are not interchangeable with other formulations of oral meloxicam even if the total milligram strength is the same (b) (4)

VIVLODEX (Meloxicam) capsules have not shown equivalent systemic exposure to other formulations of oral meloxicam. (b) (4) do not substitute similar dosing strengths of other meloxicam products [see *Clinical Pharmacology (12.3)*].

(b) (4)

USE IN SPECIAL POPULATIONS

12.3 Pharmacokinetics

The relative bioavailability of VIVLODEX 10 mg capsules compared to meloxicam 15 mg tablets was assessed in 28 healthy subjects under fasted and fed conditions in a single-dose crossover study.

VIVLODEX 10 mg capsules do not result in an equivalent systemic exposure compared to 15 mg meloxicam tablets. When taken under fasted conditions, a 33% lower dose of meloxicam in VIVLODEX 10 mg capsules resulted in a 33% lower overall systemic exposure (AUC_{inf}) and a comparable mean peak plasma concentration (C_{max}) to meloxicam 15 mg tablets. The median time to reach maximum plasma concentration (T_{max}) occurred earlier for VIVLODEX capsules (2 hours for both 5 mg and 10 mg) than for meloxicam tablets (4 hours for 15 mg).

7 DRUG INTERACTIONS

(b) (4)

Aspirin

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

4.0 Appendices

4.1 Sponsor's Proposed Label

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

4.2 Individual Study Synopses:

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

4.2.1 Study Designs:

MELI-12-04: Relative bioavailability (BA), dose-proportionality and food effect study. This study was conducted with commercial scale formulation and it fulfills the clinical pharmacology information of the proposed product from regulatory requirement perspective.

4.2.2 Study Synopses

Study MELI-12-04

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ABBREVIATIONS

ACE	angiotensin-converting enzyme
AE	adverse event
ANOVA	analysis of variance
AUC	area under the concentration-time curve
AUC _{0-∞}	area under the concentration-time curve from time 0 extrapolated to infinity
AUC _{0-t}	area under the concentration-time curve from time 0 to time of the last quantifiable concentration
BSA	body surface area
CI	confidence interval
C _{max}	maximum plasma concentration
COX	cyclooxygenase
CV	cardiovascular
ESRD	end-stage renal disease
FDA	Food and Drug Administration
GI	gastrointestinal
GMR	geometric mean ratio
IM	intramuscular(ly)
IND	Investigational New Drug
Iroko	Iroko Pharmaceuticals, LLC
IV	intravenous(ly)
LFT	liver function test
Max	maximum
Min	minimum
MRHD	maximum recommended human dose
NDA	New Drug Application
NSAID	nonsteroidal anti-inflammatory drug
OA	osteoarthritis
PD	pharmacodynamic or pharmacodynamics

PI	Prescribing Information
PK	pharmacokinetic or pharmacokinetics
POC	proof-of-concept
RA	rheumatoid arthritis
SD	standard deviation
$t_{1/2}$	terminal elimination half-life
t_{max}	time to achieve maximum plasma concentration
US	United States
Vivlodex™ Capsules	Meloxicam (established name) Vivlodex Capsules is the proposed proprietary name (formerly referred to as Meloxicam (b)(4) Capsules) and is a trademark of Iroko Pharmaceuticals, LLC
λ_z	terminal elimination rate constant

DEFINITIONS OF TERMS

Pilot Formulation	Vivlodex Capsules formulation used in the non-IND pilot pharmacokinetic (PK) (QP09C03) clinical trial
Proof-of-Concept Formulation or POC Formulation	Vivlodex Capsules formulation used in the Initial IND PK (MEL1-11-01) clinical trial
Commercial Formulation	Vivlodex Capsules formulation used in the definitive PK (MEL1-12-04) and Phase 3 (MEL3-12-02 and MEL3-12-03) clinical trials
Pilot PK trial	Term used to refer to Trial QP09C03 (Australia)
Initial IND PK trial	Term used to refer to IND Trial MEL1-11-01
Definitive PK trial	Term used to refer to IND Trial MEL1-12-04
Pivotal Phase 3 trial	Term used to refer to IND Trial MEL3-12-02
Long-term safety trial	Term used to refer to IND Trial MEL3-12-03

2.7.2 SUMMARY OF CLINICAL PHARMACOLOGY STUDIES

2.7.2.1 Background and Overview

2.7.2.1.1 Introduction

Meloxicam is a nonsteroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic, and antipyretic activities. Like other NSAIDs, the mechanism of action of meloxicam is thought to be related to inhibition of prostaglandin synthetase (cyclooxygenase [COX]). Mobic® (meloxicam) (Boehringer Ingelheim, New Drug Application [NDA] 020938) was approved by the United States (US) Food and Drug Administration (FDA) in 2000, and is available for oral administration in tablet form and as a suspension for the relief of the signs and symptoms of osteoarthritis (OA), rheumatoid arthritis (RA), and pauciarticular- or polyarticular-course juvenile RA in patients 2 years of age and older ([Mobic US Prescribing Information \[PI\], 2012](#)).

Like other NSAIDs, the risk of serious cardiovascular (CV) and gastrointestinal (GI) adverse effects such as CV thrombotic events, and bleeding ulcers and ulcers in the stomach and intestine may limit the use of meloxicam ([Scheiman JM et al, 2007](#) and [Tomisato W et al, 2004](#)). These adverse effects are dose dependent and occur more frequently at higher doses ([Henry D et al, 1996](#) and [Chan AT et al, 2006](#)). It is postulated that a reduction in meloxicam dose compared with currently marketed meloxicam oral drug products may lead to improved tolerability.

Vivlodex™ (meloxicam) Capsules are a new meloxicam drug product under development by Iroko Pharmaceuticals, LLC (Iroko) for the management of OA pain. SoluMatrix Fine Particle Technology™¹ is used to reduce drug particle sizes to enhance the rates of dissolution and absorption of meloxicam from the GI tract. The application of SoluMatrix Fine Particle Technology™ permits dose reduction of meloxicam that could provide efficacy with the potential for improved tolerability compared with currently marketed meloxicam products.

2.7.2.1.2 Overview of Vivlodex Capsules Clinical Trials

As agreed during the Pre-Phase 3 Meeting ([1.6.3 Pre-Phase 3 Meeting Minutes](#)), Vivlodex Capsules are being submitted as a 505(b)(2) NDA. The application relies on results from Vivlodex Capsules clinical trials and is supported by previous pharmacokinetic, efficacy, and safety findings for meloxicam. The core clinical development program supporting the 505(b)(2) NDA submission for Vivlodex Capsules 5 mg and 10 mg for the management of OA pain consists of 3 clinical trials:

- [MEL1-12-04](#): Phase 1 relative bioavailability, 4-period, 4-treatment, 4-sequence, single-dose, crossover trial of Vivlodex Capsules 5 mg and 10 mg (Commercial

¹ SoluMatrix Fine Particle Technology™ is a trademark of iCeutica Inc., and this technology is licensed to Iroko for exclusive use in NSAIDs.

Formulation) and Mobic 15 mg tablets in healthy subjects under fed and fasted conditions

- [MEL3-12-02](#): Phase 3 double-blind, placebo-controlled, fixed-dose efficacy and safety trial of Vivlodex Capsules 5 mg and 10 mg (Commercial Formulation) in subjects with pain due to OA of the knee or hip
- [MEL3-12-03](#): Phase 3 open-label safety trial of Vivlodex Capsules 10 mg (Commercial Formulation) in subjects with pain due to OA of the knee or hip

During the development of Vivlodex Capsules, 2 additional Phase 1 PK trials were conducted using a Pilot Formulation and a Proof-of-Concept (POC) Formulation. Data from these trials are submitted as supportive information only. [MEL1-11-01](#) was a Phase 1, single-dose, relative bioavailability trial using Vivlodex Capsules 6 mg under fasted conditions and 12 mg (2×6 mg) and Mobic 15 mg tablets in healthy subjects under fed and fasted conditions. A Phase 1 Pilot PK Trial ([QP09C03](#)), conducted by the previous sponsor in Australia, evaluated the relative bioavailability of Vivlodex Capsules 7.5 mg and Mobic capsules 7.5 mg in healthy subjects under fed and fasted conditions. This trial was not conducted under a US Investigational New Drug (IND) application.

Efficacy and safety findings from trials [MEL3-12-02](#) and [MEL3-12-03](#) are reviewed in [2.7.3 Summary of Clinical Efficacy](#) and [2.7.4 Summary of Clinical Safety](#).

2.7.2.1.2.1 Overview of the Clinical Pharmacology Program

The aim of the Vivlodex Capsules clinical pharmacology program was to describe the pharmacokinetic properties of Vivlodex Capsules in comparison with the Reference Drug, Mobic 15 mg tablets. According to the [Mobic US PI \(2012\)](#), peak meloxicam plasma concentrations occur between 4 to 5 hours following administration of a single oral dose of Mobic tablets (7.5 mg or 15 mg) under fasted conditions, indicating prolonged drug absorption. A second meloxicam concentration peak has been described approximately 12 to 14 hours postdose. Following a single oral Mobic dose of 30 mg, the absolute bioavailability of meloxicam capsules was 89% compared with a 30 mg intravenous (IV) bolus injection. Meloxicam is extensively metabolized in the liver, and in vitro studies have indicated that CYP2C9 (cytochrome P450 metabolizing enzyme) has an important role in its metabolism. Meloxicam is eliminated by hepatic metabolism and renal, biliary, and/or enteral excretion. The mean half-life of meloxicam is approximately 15 to 20 hours, and plasma clearance ranges from 7 to 9 mL/min. With multiple dosing, steady-state concentrations were reached by Day 5 ([Mobic US PI, 2012](#)).

The pharmacokinetic properties of Vivlodex Capsules have been evaluated in two Phase 1 crossover trials conducted by Iroko ([MEL1-11-01](#) and [MEL1-12-04](#)) and a Phase 1 Pilot PK crossover trial ([QP09C03](#)) conducted by the previous sponsor. All three Phase 1 trials evaluated the relative bioavailability of meloxicam following dosing with Vivlodex Capsules (Test product) compared with Mobic tablets or capsules (Reference product) in healthy subjects. Dose proportionality and the effect of food on the rate and extent of meloxicam absorption from Vivlodex Capsules were evaluated in trials [MEL1-11-01](#) (6 mg and 12 mg) and [MEL1-12-04](#) (5 mg and 10 mg).

Formulation development of Vivlodex Capsules included 3 formulations: a Pilot Formulation used in [QP09C03](#), a POC Formulation used in [MEL1-11-01](#), and the Commercial Formulation. Subjects in the Definitive PK trial, [MEL1-12-04](#), and in the completed Phase 3 clinical trials were administered the Commercial Formulation of Vivlodex Capsules, which reflected changes to the dosing strength and the manufacturing process. A summary of the Phase 1 clinical trial designs, trial objectives, dosing regimens and durations, treatment groups, baseline demographics, and pharmacokinetic assessments is provided in [Table 2.7.2.1.2.1-1](#).

Clinical pharmacology information from published studies relevant to the interpretation of Vivlodex Capsules pharmacokinetics and pharmacodynamics is also described in this summary. The literature search strategy and criteria for selection of relevant articles, as well as a full list of all the articles selected, are provided in [5.4 Literature References](#).

Table 2.7.2.1.2.1-1 Summary of Vivlodex Capsules Phase 1 Clinical Trials

	QP09C03	MEL1-11-01	MEL1-12-04
Trial dates	21JUL2009 to 20AUG2009	08FEB2012 to 29APR2012	21May2013 to 23AUG2013
Vivlodex Capsules Formulation	Pilot	POC	Commercial
Trial design	Phase 1	Phase 1	Phase 1
	Single-dose	Single-dose	Single-dose
	4-way crossover	5-way crossover	4-way crossover
	Relative bioavailability and PK	Relative bioavailability, food effect, dose proportionality, and PK	Relative bioavailability, food effect, dose proportionality, and PK
Trial objectives	<ul style="list-style-type: none"> Determine the rate and extent of absorption of Vivlodex Capsules 7.5 mg (Test) vs Mobic capsules 7.5 mg (Reference) under fasted conditions Determine the rate and extent of absorption of Vivlodex Capsules 7.5 mg (Test) vs Mobic capsules 7.5 mg (Reference) under fed conditions 	<ul style="list-style-type: none"> Determine relative bioavailability following administration of Vivlodex Capsules 12 mg (Test) vs Mobic 15 mg tablets (Reference) under fasted conditions Determine dose proportionality of 6 mg and 12 mg Vivlodex Capsules Determine the effect of food on the rate and extent of absorption of Vivlodex Capsules 12 mg vs Mobic 15 mg tablets 	<ul style="list-style-type: none"> Determine relative bioavailability following administration of Vivlodex Capsules 10 mg (Test) vs Mobic 15 mg tablets (Reference) under fasted conditions Determine dose proportionality of 5 mg and 10 mg Vivlodex Capsules Determine the effect of food on the rate and extent of absorption of Vivlodex Capsules 10 mg
Trial population	Healthy adults	Healthy adults	Healthy adults
Dosing regimen and duration	4 sequential single-dose dosing periods followed by 7-day washout period	5 sequential single-dose dosing periods followed by 14-day washout period	4 sequential single-dose dosing periods followed by 14-day washout period
Treatment groups	<ul style="list-style-type: none"> Vivlodex Capsules 7.5 mg (Test) Fasted Mobic 7.5 mg 	<ul style="list-style-type: none"> Vivlodex Capsules 12 mg (2×6 mg) (Test) Fasted 	<ul style="list-style-type: none"> Vivlodex Capsules 10 mg (Test) Fasted Vivlodex Capsules

Table 2.7.2.1.2.1-1 Summary of Vivlodex Capsules Phase 1 Clinical Trials

	QP09C03	MEL1-11-01	MEL1-12-04
	capsules (Reference) Fasted <ul style="list-style-type: none"> Vivlodex Capsules (Test) 7.5 mg Fed Mobic capsules (Reference) 7.5 mg Fed 	<ul style="list-style-type: none"> Vivlodex Capsules 12 mg (2×6 mg) Fed Vivlodex Capsules 6 mg Fasted Mobic 15 mg tablets (Reference) Fasted Mobic 15 mg tablets (Reference) Fed 	10 mg (Test) Fed <ul style="list-style-type: none"> Vivlodex Capsules 5 mg (Test) Fasted Mobic 15 mg tablets (Reference) Fasted
Total subjects enrolled	14	28	28
Demographics	Male: 9 (64.3%) Female: 5 (35.7%) Mean age: 25.1 years (18 to 47 years)	Male: 21 (75.0%) Female: 7 (25.0%) Mean age: 34.3 years (21 to 53 years)	Male: 14 (50.0%) Female: 14 (50.0%) Mean age: 33.8 years (20 to 54 years)
Pharmacokinetic assessments	Pharmacokinetic variables included: <ul style="list-style-type: none"> AUC_{0-t} AUC_{0-∞} C_{max} t_{max} λ_z t_{1/2} 	Pharmacokinetic variables included: <ul style="list-style-type: none"> AUC_{0-t} AUC_{0-∞} C_{max} t_{max} λ_z t_{1/2} 	Pharmacokinetic variables included: <ul style="list-style-type: none"> AUC_{0-t} AUC_{0-∞} C_{max} t_{max} λ_z t_{1/2}

Data source: 5.3.1.2 QP09C03 CSR, MEL1-11-01 CSR, and MEL1-12-04 CSR.

Abbreviations: λ_z = terminal elimination rate constant; AUC_{0-∞} = area under the concentration time curve from time 0 extrapolated to infinity; AUC_{0-t} = area under the concentration time curve from time 0 to the time of the last sample with a quantifiable concentration; C_{max} = maximum plasma concentration; PK = pharmacokinetics; t_{1/2} = terminal elimination half-life; t_{max} = time to achieve maximum plasma concentration

2.7.2.2 Summary of Results of Individual Trials

2.7.2.2.1 Methodology

Clinical trial QP09C03 was a single-center, single-dose, randomized, open-label, 4-period, 4-treatment crossover Phase 1 pilot trial conducted in Australia to evaluate the relative bioavailability of meloxicam from Vivlodex Capsules 7.5 mg versus Mobic 7.5 mg capsules in healthy subjects.

MEL1-11-01 and MEL1-12-04 were single-center, single-dose, randomized, open-label, crossover Phase 1 trials designed to evaluate the relative bioavailability, food effect, and dose proportionality of meloxicam from Vivlodex Capsules versus Mobic tablets in healthy subjects. Vivlodex Capsules at dosages of 6 mg and 12 mg (MEL1-11-01) and 5 mg and 10 mg (MEL1-12-04) were compared to Mobic 15 mg tablets. MEL1-11-01 was a 5-period, 5-treatment crossover trial; MEL1-12-04 was a 4-period, 4-treatment crossover trial.

Healthy adult male and female subjects, between 18 to 55 years of age, who met all eligibility criteria, including a body weight of ≥ 110 pounds (50 kg) and body mass index between 18 to 30 kg/m², were randomized equally to different sequences of single-dose trial drug administration. Each subject received trial drug in the order of the assigned sequence according to the randomization code. Subjects entered the clinic on Day 0 of the first dosing period and fasted overnight for at least 10 hours. On the morning of Day 1, subjects were administered the Test or Reference products under fasted conditions or following a high-fat meal, depending on the treatment assignment. Blood samples for the evaluation of meloxicam plasma concentrations were obtained predose and at predefined time points up to 48 (QP09C03), 72 (MEL1-11-01), or 96 hours (MEL1-12-04) after dosing. Subjects were discharged after the final blood collection, and were asked to return to the clinic after a 7-day (QP09C03) or 14-day (MEL1-11-01 and MEL1-12-04) washout period to continue the trial drug administration sequence for the remaining periods (Dosing Periods 2 through 4 for trials QP09C03 and MEL1-12-04, and Dosing Periods 2 through 5 for MEL1-11-01). A blood sample for safety assessments was collected with the last blood sample for pharmacokinetic analysis collected in the last treatment period.

The pharmacokinetic parameters analyzed in each of the trials included the maximum meloxicam plasma concentration (C_{max}), time to achieve maximum meloxicam concentration (t_{max}), area under the meloxicam concentration-time curve (AUC) from time 0 to the time of the last sample with a quantifiable concentration (AUC_{0-t}), AUC from time 0 extrapolated to infinity ($AUC_{0-\infty}$), apparent terminal elimination rate constant (λ_z), and apparent terminal elimination half-life ($t_{1/2}$). For the meloxicam pharmacokinetic parameters C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$, a mixed model analysis of variance (ANOVA) was used to test the significance of the effects of sequence, period, and treatment for each. A 90% confidence interval (CI) for the treatment ratio was obtained by taking the antilogarithm of the 90% CI endpoints for the mean difference (Test – Reference). Statistical equivalence and comparability of treatments were assessed by the geometric means ratio (GMR; “Test” to “Reference”) with 90% CI for the natural log transformed parameters (C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$). Treatments were considered statistically equivalent for a given pharmacokinetic parameter if the 90% CI for the GMR fell within the equivalence limits of 0.8 to 1.25.

Dose proportionality for the 6 mg and 12 mg, and the 5 mg and 10 mg doses of Vivlodex Capsules was also assessed (trials MEL1-11-01 and MEL-12-04). The dose-normalized meloxicam AUCs and C_{\max} were natural log-transformed and analyzed using a linear mixed model to test the significance of the effects of sequence, period, and treatment. Evidence of dose proportionality was indicated if the 90% CI for the GMR was within 0.8 to 1.25. Additionally, for the 5 mg and 10 mg doses in clinical trial MEL1-12-04, similar analysis of dose proportionality using ANOVA was performed using nondose-normalized AUC and C_{\max} . In this case, evidence of dose proportionality was indicated if the estimated GMR was close to 2.00.

The effect of food on Vivlodex Capsules absorption was evaluated in MEL1-12-04 (10 mg) and MEL1-11-01 (12 mg) using estimates of the rate of absorption (C_{\max} and t_{\max}) and the overall extent of absorption (AUC_{0-t} and $AUC_{0-\infty}$). For purposes of the food effect analyses, the fed state was designated as the “Test” treatment and the fasting state was the “Reference” treatment. Absence of a food effect on bioavailability measures (ie, pharmacokinetic parameters were statistically equivalent for the fed and fasted state) was concluded if the 90% CI for the GMR between treatments (Test to Reference) was within 0.8 to 1.25 for $AUC_{0-\infty}$, t_{\max} , and C_{\max} .

2.7.2.2.2 Clinical Trial MEL1-12-04

A Randomized, 4-Period, 4-Treatment, 4-Sequence, Single-Dose, Crossover, Pharmacokinetic Trial of Meloxicam SoluMatrix™ Capsules 5 mg and 10 mg and Mobic® 15 mg in Healthy Subjects

A total of 28 subjects received at least 1 dose of trial drug and were included in the full analysis set. Twenty-five subjects completed all 4 trial periods. Three subjects did not complete the trial: 1 subject withdrew due to a protocol violation, 1 subject withdrew due to an adverse event (AE), and 1 subject was lost to follow-up. The population was evenly distributed between males and females with a mean age of 33.8 years, and ages ranging from 20.0 to 54.0 years. Complete subject disposition and demographic information are provided in 2.7.4 Summary of Clinical Safety, Section 2.7.4.2.1 and Table 2.7.4.1.2-1, respectively. Pharmacokinetic parameters are summarized in Table 2.7.2.2.2-1 and described in further detail in the sections that follow.

Table 2.7.2.2-1 Summary of the Meloxicam Pharmacokinetic Parameters (MEL1-12-04)

Pharmacokinetic Parameter	Mean±SD (n)			
	Vivlodex Capsules 10 mg Fasted	Vivlodex Capsules 10 mg Fed	Vivlodex Capsules 5 mg Fasted	Mobic 15 mg Tablets Fasted
C _{max} (ng/L)	1252.8±254.2 (27)	973.9±165.4 (26)	642.4±138.5 (26)	1288.8±424.4 (27)
t _{max} (hour) ^a	2.00 (1.00, 5.00) (27)	5.00 (1.50, 16.02) (26)	2.00 (0.50, 4.07) (26)	4.00 (2.02, 8.00) (27)
AUC _{0-t} (hour*ng/mL)	28190.5±9264.7 (27)	26681.2±9748.0 (26)	14206.5±5415.3 (26)	39093.8±16500.2 (27)
AUC _{0-∞} (hour*ng/mL)	29173.0±11042.1 (26)	27145.9±11469.5 (24)	13610.5±3342.7 (24)	40875.6±11733.5 (23)
t _{1/2} (hour)	22.04±10.08 (27)	22.27±9.88 (26)	22.32±10.91 (26)	23.64±10.04 (27)

Data source: 5.3.1.2 MEL1-12-04 CSR, Table 14.2.2.

Abbreviations: AUC_{0-∞} = area under the concentration time curve from time 0 extrapolated to infinity; AUC_{0-t} = area under the concentration time curve from time 0 to the time of the last sample with a quantifiable concentration; C_{max} = maximum plasma concentration; SD = standard deviation; Min = minimum; Max = maximum; t_{1/2} = terminal elimination half-life; t_{max} = time to achieve maximum concentration

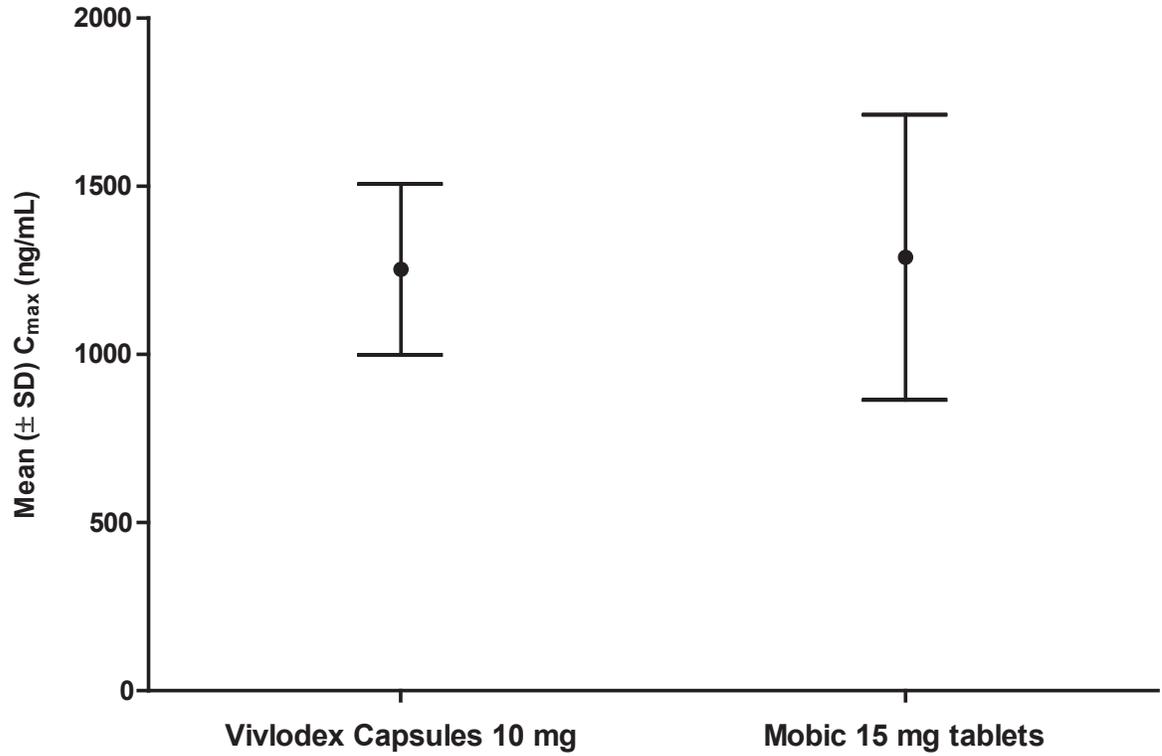
^a t_{max} is presented as median values (Min, Max)

2.7.2.2.2.1 Rate and Extent of Absorption

Mean (standard deviation [SD]) C_{max} was similar for Vivlodex Capsules 10 mg (1252.8 [254.2] ng/mL) and Mobic 15 mg tablets (1288.8 [424.4] ng/mL). The SD for meloxicam C_{max} observed for Vivlodex Capsules 10 mg under fasted conditions was lower than that observed for Mobic 15 mg tablets, suggesting that the Vivlodex Capsules Commercial Formulation decreased variability of meloxicam absorption compared with Mobic tablets (Figure 2.7.2.2.2.1-1).

Mean plasma meloxicam concentrations over time under fasted conditions are presented for the Vivlodex Capsules 5 mg and 10 mg and the Mobic 15 mg tablets groups in Figure 2.7.2.2.2.1-2.

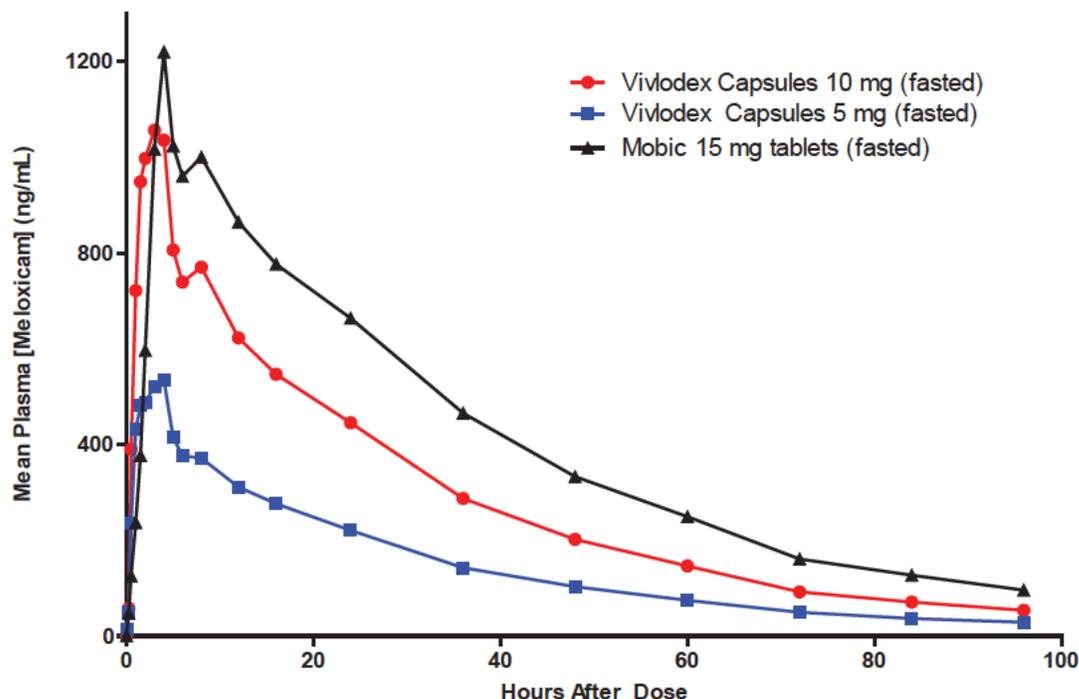
Figure 2.7.2.2.1-1 Mean (\pm SD) Meloxicam C_{max} in Fasted Subjects Following Administration of Vivlodex Capsules 10 mg and Mobic 15 mg Tablets (MEL1-12-04)



Data source: 5.3.1.2 MEL1-12-04 CSR, Table 14.2.2.

Abbreviations: C_{max} = maximum plasma concentration; SD = standard deviation

Figure 2.7.2.2.1-2 Mean Plasma Meloxicam Concentrations in Fasted Subjects Following Administration of Vivlodex Capsules 10 mg and 5 mg and Mobic 15 mg Tablets (MEL1-12-04)



Data source: 5.3.1.2 MEL1-12-04 CSR, Table 14.2.1.

Absorption of meloxicam in the fasted state was faster from Vivlodex Capsules 5 mg and 10 mg compared with Mobic 15 mg tablets in trial MEL1-12-04. The median t_{max} of Vivlodex Capsules 5 mg and 10 mg (2.00 hours) was half the median t_{max} of Mobic 15 mg tablets (4.00 hours). A secondary peak of plasma meloxicam concentrations was noted at 8 hours for all the fasted treatments, after which plasma meloxicam concentrations declined mono-exponentially.

The GMR for the comparison of meloxicam C_{max} for Vivlodex Capsules 10 mg and Mobic 15 mg tablets under fasted conditions was 1.08, with the upper bound of the 90% CI (0.91, 1.29) just outside the equivalence acceptance limits of 0.8 to 1.25. Of note, following administration of Mobic 15 mg tablets under fasted conditions, 1 subject (Subject 15) had meloxicam plasma concentrations that were inconsistent with the values observed in other subjects. A majority of the postdose meloxicam plasma concentrations for Subject 15 following administration of Mobic 15 mg tablets were below the quantifiable limit. For this reason, a post hoc sensitivity analysis was conducted that excluded data from Subject 15 in the Mobic 15 mg tablets fasted group to examine the effect of these data on the primary relative bioavailability results. After exclusion of the data from Subject 15, the resulting

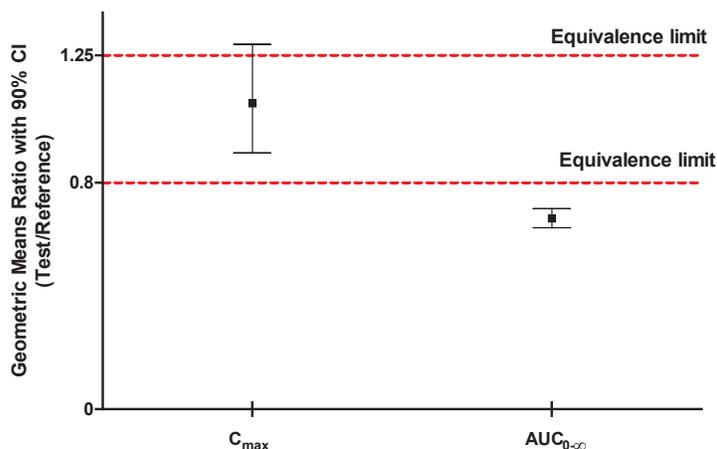
GMR was 0.947, and the 90% CI for the comparison of C_{\max} values (0.88, 1.02) was within the equivalence limits (Table 2.7.2.2.2-1).

In contrast, the overall extent of exposure to meloxicam ($AUC_{0-\infty}$) following administration of Vivlodex Capsules 10 mg was approximately 33% lower than that from Mobic 15 mg tablets under fasting conditions. This was reflected in the GMR (90% CI) of 0.67 (0.64, 0.71) for the comparison of meloxicam $AUC_{0-\infty}$ of Vivlodex Capsules 10 mg and Mobic 15 mg tablets in fasted subjects. Calculation of the $AUC_{0-\infty}$ excluded subject data that required extrapolation $\geq 21\%$ therefore, the data from Subject 15 were excluded from the $AUC_{0-\infty}$ comparison. The GMR and 90% CI values were outside the equivalence limits of 0.8 to 1.25, indicating a statistical difference in the total systemic exposure to meloxicam from the drug products.

The initial comparison of meloxicam AUC_{0-t} of Vivlodex Capsules 10 mg and Mobic 15 mg tablets in fasted subjects resulted in a GMR (90% CI) of 0.82 (0.68, 1.00). The comparison, however, included aberrant plasma concentration data from Subject 15. The results of a post hoc analysis that excluded the data from Subject 15 demonstrated a statistical difference in the total systemic exposure to meloxicam from the two drug products as measured by AUC_{0-t} . The post hoc AUC_{0-t} comparison GMR (90% CI) was 0.70 (0.66, 0.74), which fell outside the equivalence limit of 0.8 to 1.25.

The GMRs from the comparisons of meloxicam C_{\max} and $AUC_{0-\infty}$ with 90% CIs are presented graphically in Figure 2.7.2.2.2.1-3. Results of the statistical analysis of relative bioavailability of Vivlodex Capsules 10 mg and Mobic 15 mg tablets in fasted subjects, including the GMR and corresponding 90% CIs, are presented in Table 2.7.2.2.3.1-1.

Figure 2.7.2.2.2.1-3 GMR (90% CI) for Comparison of Meloxicam C_{\max} and $AUC_{0-\infty}$ in Fasted Subjects Following Administration of Vivlodex Capsules 10 mg or Mobic 15 mg Tablets (MEL1-12-04)



Data source: 5.3.1.2 MEL1-12-04 CSR, Table 14.2.3.1.

Abbreviations: $AUC_{0-\infty}$ = area under the concentration time curve from time 0 extrapolated to infinity; CI = confidence interval; C_{\max} = maximum plasma concentration; GMR = geometric mean ratio

Table 2.7.2.2.1-1 Statistical Analysis of Relative Bioavailability in Fasted Subjects for Meloxicam Plasma Pharmacokinetic Parameters – Vivlodex Capsules 10 mg and Mobic 15 mg Tablets (MEL1-12-04)

Pharmacokinetic Parameter	Least Squares Geometric Mean		GMR ^c	90% CI
	Vivlodex Capsules 10 mg Fasted n=27 ^a	Mobic 15 mg Tablets Fasted n=27 ^b		
C _{max} (ng/mL)	1225.4	1135.0	1.08	0.91, 1.29
t _{max} (hour) ^d	2.00	4.00	--	--
AUC _{0-t} (hour*ng/mL)	26971.7	32793.9	0.82	0.68, 1.00
AUC _{0-∞} (hour*ng/mL)	28041.6	41616.8	0.67	0.64, 0.71

Data source: 5.3.1.2 MEL1-12-04 CSR, Table 14.2.3.1.

Abbreviations: AUC_{0-∞} = area under the concentration time curve from time 0 extrapolated to infinity; AUC_{0-t} = area under the concentration time curve from time 0 to the time of the last sample with a quantifiable concentration; CI = confidence interval; C_{max} = maximum plasma concentration; GMR = ratio of the geometric means

^a For AUC_{0-∞} estimation n=26.

^b For AUC_{0-∞} estimation n=23.

^c GMR is the ratio of least squares geometric means for Vivlodex Capsules 10 mg Fasted to Mobic 15 mg tablets Fasted.

^d Median.

2.7.2.2.2 Dose Proportionality

A statistically significant dose proportional relationship for meloxicam AUC_{0-∞}, AUC_{0-t}, and C_{max} was demonstrated following administration of 5 mg and 10 mg Vivlodex Capsules under fasted conditions. The dose-normalized GMRs of meloxicam for all 3 parameters were close to 1.0, and the 90% CIs around the GMRs were within the 0.8 to 1.25 equivalence limits (5.3.1.2 MEL1-12-04 CSR, Table 14.2.4 and Figure 14.2.5).

Similar to the dose-normalized results, non-dose normalized meloxicam AUC_{0-t}, AUC_{0-∞}, and C_{max} analyses demonstrated a dose-proportional increase in overall systemic absorption, with ratios of non-dose-normalized geometric means that were close to 2.00, defining a linear dose effect (5.3.1.2 MEL1-12-04 CSR, Table 14.2.5). The results of the statistical analysis to assess dose proportionality of the 5 mg and 10 mg doses of Vivlodex Capsules using dose-normalized AUC_{0-t}, AUC_{0-∞}, and C_{max} values are presented in Table 2.7.2.2.2.2-1.

Table 2.7.2.2.2-1 Statistical Analysis of Dose Proportionality for Dose-Normalized Meloxicam Plasma Pharmacokinetic Parameters – (MEL1-12-04)

Pharmacokinetic Parameter	Least Squares Geometric Mean		GMR ^c	90% CI
	Vivlodex Capsules 10 mg Fasted n=27 ^a	Vivlodex Capsules 5 mg Fasted n=26 ^b		
C _{max} (ng/mL)	123.1	125.4	0.98	0.94, 1.03
AUC _{0-t} (hour*ng/mL)	2721.4	2734.5	1.00	0.96, 1.04
AUC _{0-∞} (hour*ng/mL)	2785.8	2782.6	1.00	0.95, 1.05

Data source: 5.3.1.2 MEL1-12-04 CSR, Table 14.2.4.

Abbreviations: AUC_{0-∞} = area under the concentration time curve from time 0 extrapolated to infinity; AUC_{0-t} = area under the concentration time curve from time 0 to the time of the last sample with a quantifiable concentration; CI = confidence interval; C_{max} = maximum plasma concentration; GMR = ratio of the geometric means

^a For AUC_{0-∞} estimation n=26.

^b For AUC_{0-∞} estimation n=24.

^c GMR is the ratio of least squares geometric means for Vivlodex Capsules 10 mg Fasted to Vivlodex Capsules 5 mg Fasted.

2.7.2.2.2.3 Food Effect

Administration of Vivlodex Capsules 10 mg under fed conditions resulted in a decreased rate of meloxicam absorption (C_{max}). The GMR (90% CI) for the comparison of meloxicam C_{max} following administration in fed and fasted subjects was 0.78 (0.66, 0.94) (Table 2.7.2.2.3-1), indicating that the C_{max} in fed subjects was decreased by approximately 22% compared with the C_{max} in fasted subjects (5.3.1.2 MEL1-12-04 CSR, Table 14.2.6). Parametric and nonparametric analyses of t_{max} showed a significant delay (approximately 3 hours) for the fed Vivlodex Capsules 10 mg group compared with the fasted Vivlodex Capsules 10 mg group (Table 2.7.2.2.3-1, 5.3.1.2 MEL1-12-04 CSR, Table 14.2.7).

The GMR (90% CI) of meloxicam AUC_{0-∞} values following administration of Vivlodex Capsules 10 mg in fed versus fasted subjects was 0.92 (0.87, 0.96), indicating no statistical differences in the total systemic exposure to meloxicam. The GMR (90% CI) for meloxicam AUC_{0-t} values in fed versus fasted subjects was 0.94 (0.77, 1.14). Though the lower bound of the 90% CI was slightly outside the equivalence limits of 0.8 to 1.25, the results of the AUC_{0-t} comparison were generally consistent with those of AUC_{0-∞}. These small differences combined with the estimation of the meloxicam AUC_{0-∞} following fed administration of Vivlodex Capsules 10 mg, suggest that food has a limited effect on the overall extent of meloxicam exposure.

Results of the statistical analysis of food effect for Vivlodex Capsules 10 mg in fed and fasted subjects, including the GMRs and corresponding 90% CIs, are presented in Table 2.7.2.2.3-1. The nonparametric statistical analysis of the food effect on t_{max} is presented in Table 2.7.2.2.3-2. Mean meloxicam plasma concentrations over time for Vivlodex Capsules 10 mg under fed and fasted conditions are presented in Figure 2.7.2.2.3-1.

Table 2.7.2.2.3-1 Statistical Analysis of Food Effect for Meloxicam Plasma Pharmacokinetic Parameters – Vivlodex Capsules 10 mg in Fasted and Fed Subjects (MEL1-12-04)

Pharmacokinetic Parameter	Least Squares Geometric Mean		GMR ^c	90% CI
	Vivlodex Capsules 10 mg Fasted n=27 ^a	Vivlodex Capsules 10 mg Fed n=26 ^b		
C_{max} (ng/mL)	1225.4	959.7	0.78	0.66, 0.94
AUC_{0-t} (hour*ng/mL)	26971.7	25249.7	0.94	0.77, 1.14
$AUC_{0-\infty}$ (hour*ng/mL)	28041.6	25644.6	0.92	0.87, 0.96
t_{max} (hour)	2.22	5.18	2.33	1.88, 2.90

Data source: 5.3.1.2 MEL1-12-04 CSR, Table 14.2.6.

Abbreviations: $AUC_{0-\infty}$ = area under the concentration time curve from time 0 extrapolated to infinity; AUC_{0-t} = area under the concentration time curve from time 0 to the time of the last sample with a quantifiable concentration; CI = confidence interval; C_{max} = maximum plasma concentration; GMR = ratio of the geometric means; t_{max} = time to achieve maximum concentration

^a For $AUC_{0-\infty}$ estimation n=26.

^b For $AUC_{0-\infty}$ estimation n=24.

^c GMR is the ratio of least squares geometric means for Vivlodex Capsules 10 mg Fasted to Vivlodex Capsules 10 mg Fed.

Values of $AUC_{0-\infty}$ with associated AUC% extrapolated $\geq 21\%$ were excluded from the statistical analysis of the effect of food.

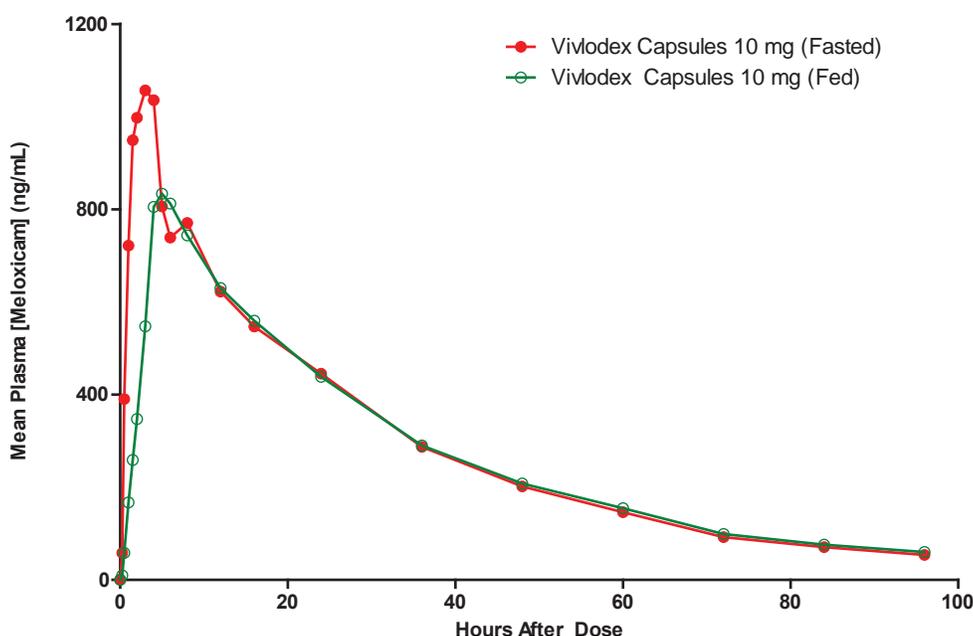
Table 2.7.2.2.3-2 Nonparametric Food Effect Analysis of t_{max} for Meloxicam - Vivlodex Capsules 10 mg in Fasted and Fed Subjects (MEL1-12-04)

Parameter (unit)	Treatment Comparison	n	Hodges-Lehman Estimate Median Difference	90% CI for Estimate of Median Difference
t_{max} (hour)	Vivlodex Capsules 10 mg Fed vs Fasted	25	3.00	(2.02, 4.01)

Data source: 5.3.1.2 MEL1-12-04 CSR, Table 14.2.7.

Abbreviations: CI = confidence interval; t_{max} = time to achieve maximum concentration

Figure 2.7.2.2.3-1 Mean Plasma Meloxicam Concentrations in Fasted and Fed Subjects Following Administration of Vivlodex Capsules 10 mg (MEL1-12-04)



Data source: 5.3.1.2 MEL1-12-04 CSR, Table 14.2.1.

2.7.2.2.2.4 Conclusions

- The meloxicam C_{max} values following administration of Vivlodex Capsules 10 mg and Mobic 15 mg tablets under fasting conditions were similar. The primary and post hoc sensitivity analyses demonstrated GMRs (90% CI) of 1.08 (0.91, 1.29) and 0.95 (0.88, 1.02), respectively, for the comparison of C_{max} between Vivlodex

Capsules 10 mg and Mobic 15 mg tablets, indicating comparability of the maximum meloxicam concentration from the drug products.

- Less variability in C_{\max} was observed following administration of Vivlodex Capsules 10 mg compared with Mobic 15 mg tablets.
- The median time to maximum meloxicam concentrations (t_{\max}) occurred 2 hours earlier following administration of Vivlodex Capsules 10 mg compared with Mobic 15 mg tablets in fasting subjects.
- Under fasted conditions, the total systemic exposure to meloxicam following administration of Vivlodex Capsules 10 mg was approximately 33% lower than that observed for Mobic 15 mg tablets based on $AUC_{0-\infty}$. The GMR and associated 90% CI were outside the equivalence limits of 0.8 to 1.25, indicating a statistical difference between the drug products.
- Vivlodex Capsules 5 mg and 10 mg were dose proportional for C_{\max} , AUC_{0-t} , and $AUC_{0-\infty}$ under fasted conditions.
- Food decreased the rate (C_{\max} and t_{\max}) but not the overall extent of meloxicam absorption ($AUC_{0-\infty}$) from Vivlodex Capsules 10 mg.

2.7.2.2.3 Clinical Trial [MEL1-11-01](#)

A Randomized, 5-Period, 5-Treatment, 5-Sequence Single-Dose Crossover, Pharmacokinetic Study of Meloxicam SoluMatrix™ Capsules 6 mg under Fasted Conditions and Meloxicam SoluMatrix™ Capsules 12 mg and Mobic® 15 mg under Fed and Fasted Conditions

Of the 29 subjects who enrolled in the trial, 28 subjects received at least 1 dose of trial drug and were included in the full analysis set. One randomized subject was withdrawn due to abnormal baseline clinical laboratory measurements prior to receiving any trial medication. Twenty-six subjects completed the trial; 1 subject withdrew due to a protocol violation and 1 subject completed all dosing periods but was considered lost to follow-up. The population was predominantly male with a mean age of 34.3 years, and ages ranging from 21.0 to 53.0 years. Complete subject disposition and demographic information are provided in the [2.7.4 Summary of Clinical Safety, Section 2.7.4.2.1](#) and [Table 2.7.4.1.2-1](#), respectively. Pharmacokinetic parameters are summarized in [Table 2.7.2.2.3-1](#) and described in further detail in the sections that follow.

Table 2.7.2.2.3-1 Summary of the Meloxicam Pharmacokinetic Parameters (MEL1-11-01)

Mean±SD (Min, Max)	Vivlodex Capsules			Mobic Tablets	
	12 mg Fasted n=27	12 mg Fed n=27	6 mg Fasted n=27	15 mg Fasted n=28	15 mg Fed n=27
C _{max} (ng/L)	1541.9±306.2 (917.0, 2219.0)	1160.2±307.2 (728.3, 1834.0)	760.4±192.8 (429.0, 1296.0)	1199.6±223.7 (790.4, 1712.0)	1338.0±307.8 (841.8, 2170.0)
t _{max} (hour) ^a	1.97 (0.97, 4.01)	5.00 (3.01, 12.00)	2.00 (0.53, 6.00)	4.02 (3.01, 23.99)	6.00 (3.98, 12.01)
AUC _{0-t} (hour*ng/mL)	33135.5± 11399.6 (21267.2, 66453.3)	31973.8±10906.5 (18909.7, 67929.5)	16274.9±5806.2 (10536.8, 38126.5)	38297.7±11824.9 (25418.2, 79566.7)	39323.1±12793.8 (25054.4, 79931.2)
AUC _{0-∞} (hour*ng/mL)	39858.7±21909.7 (22487.1, 112519.1)	38178.6±20564.1 (19206.2, 117783.0)	19141.2±9816.7 (11060.8, 56290.5)	46252.6±22378.3 (26269.2, 127114.6)	48362.4±27335.8 (28847.8, 140863.1)
λ _z (1/hour)	0.034±0.010 (0.013, 0.051)	0.035±0.013 (0.012, 0.068)	0.035±0.011 (0.015, 0.059)	0.033±0.011 (0.012, 0.057)	0.034±0.011 (0.011, 0.056)
t _{1/2} (hour)	23.32±10.43 (13.48, 54.22)	22.42±9.90 (10.13, 56.97)	22.61±8.99 (11.73, 45.04)	23.77±10.00 (12.21, 56.38)	23.61±11.71 (12.33, 62.92)

Data source: 5.3.1.2 MEL1-11-01 CSR, Table 14.2.2.

Abbreviations: λ_z = terminal elimination rate constant; AUC_{0-∞} = area under the concentration time curve from time 0 extrapolated to infinity; AUC_{0-t} = area under the concentration time curve from time 0 to the time of the last sample with a quantifiable concentration; C_{max} = maximum plasma concentration; hr = hour; Min = minimum; Max = maximum; SD = standard deviation; t_{1/2} = terminal elimination half-life; t_{max} = time to achieve maximum concentration

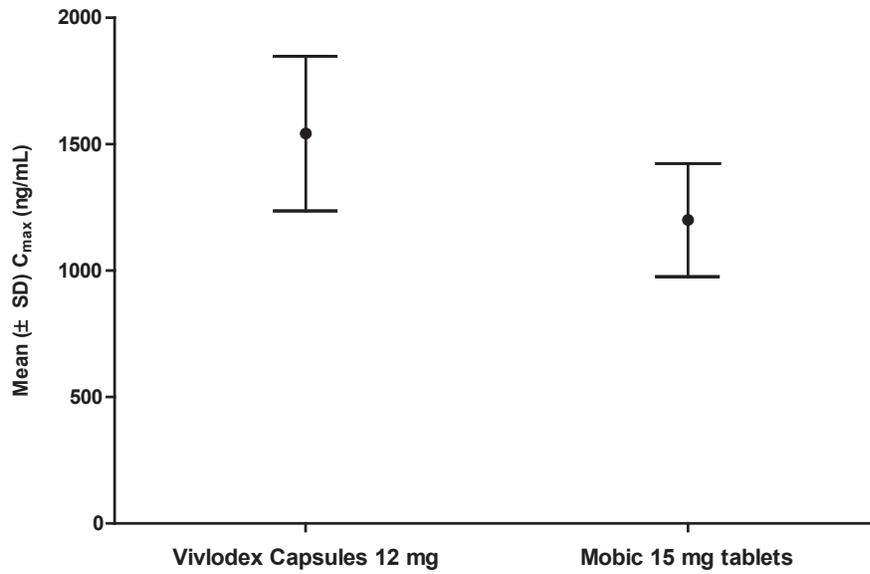
^a Median values (not mean values) are presented for t_{max}

2.7.2.2.3.1 Rate and Extent of Absorption

Vivlodex Capsules 12 mg (dosed as 2×6 mg capsules) demonstrated higher peak meloxicam plasma concentrations (C_{max}) compared with Mobic 15 mg tablets (Figure 2.7.2.2.3.1-1). The mean meloxicam C_{max} in subjects administered Vivlodex Capsules 12 mg under fasted conditions (1541.9±306.2 ng/mL) was 28% higher than the mean C_{max} for subjects following administration of Mobic 15 mg tablets (1199.6±223.7 ng/mL). The GMR (90% CI) for the comparison of C_{max} for Vivlodex Capsules 12 mg vs. Mobic 15 mg tablets was 1.28 (1.19, 1.37) (Table 2.7.2.2.3-1), indicating a trend towards significantly different meloxicam C_{max} for Vivlodex Capsules 12 mg compared with Mobic 15 mg tablets.

Mean plasma meloxicam concentrations over time under fasted conditions are presented for the Vivlodex Capsules 12 mg and 6 mg and the Mobic 15 mg tablets groups in Figure 2.7.2.2.3.1-2.

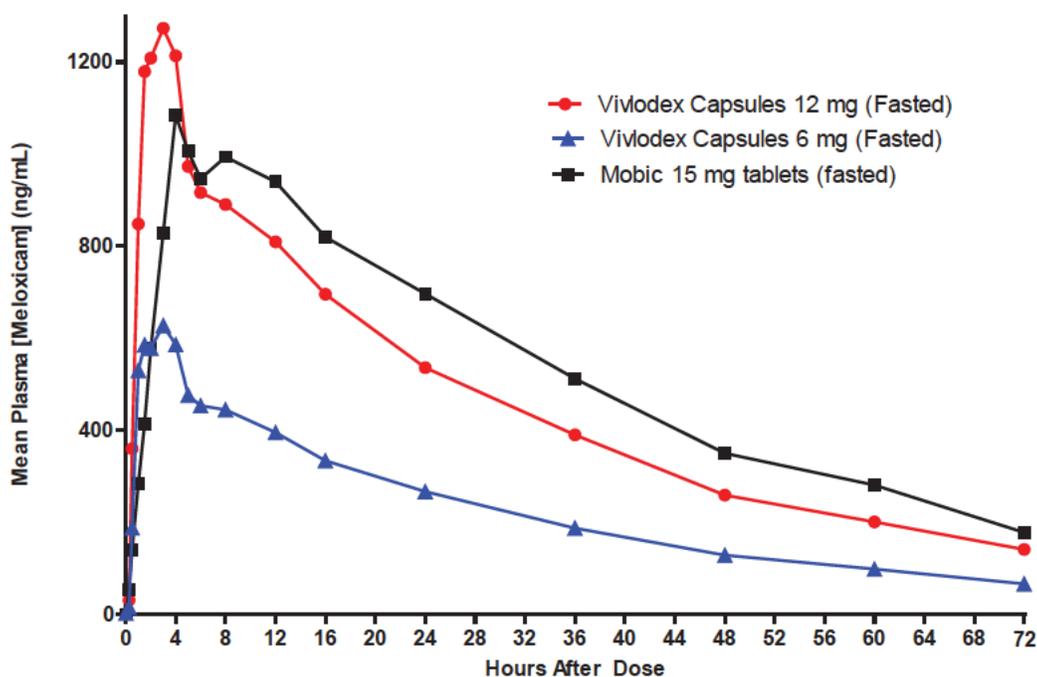
Figure 2.7.2.3.1-1 Mean (\pm SD) Meloxicam C_{max} in Fasted Subjects Following Administration of Vivlodex Capsules 12 mg and Mobic 15 mg Tablets (MEL1-11-01)



Data source: 5.3.1.2 MEL1-11-01 CSR, Table 14.2.2.

Abbreviations: C_{max} = maximum plasma concentration; SD = standard deviation

Figure 2.7.2.2.3.1-2 Mean Plasma Meloxicam Concentrations in Fasted Subjects Following Administration of Vivlodex Capsules 12 and 6 mg and Mobic 15 mg Tablets (MEL1-11-01)



Data source: 5.3.1.2 MEL1-11-01 CSR, Table 14.2.1.

In contrast to C_{max} , the overall extent of exposure to meloxicam (AUC_{0-t} and $AUC_{0-\infty}$) following administration of the Vivlodex Capsules 12 mg dose was approximately 14% lower than that observed for Mobic 15 mg tablets under fasting conditions. The GMRs and corresponding 90% CIs were 0.86 (90% CI: 0.84, 0.89) for AUC_{0-t} and 0.85 (90% CI: 0.82, 0.88) for $AUC_{0-\infty}$. Both GMR comparisons were within the bioequivalence limits of 0.8 to 1.25, indicating that the overall extent of exposure to meloxicam was similar following administration of Vivlodex Capsules 12 mg and Mobic 15 mg tablets.

Peak meloxicam plasma concentrations occurred earlier for Vivlodex Capsules 12 mg (median t_{max} =1.97 hours) than for Mobic 15 mg tablets (median t_{max} =4.02 hours) following administration to subjects under fasted conditions. The median t_{max} for Vivlodex Capsules 12 mg and Mobic 15 mg tablets are presented in Table 2.7.2.2.3-1.

Results of the statistical analysis comparing the relative bioavailability of Vivlodex Capsules 12 mg and Mobic 15 mg tablets in fasted subjects, including the GMR and corresponding 90% CIs, are presented in Table 2.7.2.2.3.1-1.

Table 2.7.2.2.3.1-1 Statistical Analysis of Relative Bioavailability in Fasted Subjects for Meloxicam Plasma Pharmacokinetic Parameters – Vivlodex Capsules 12 mg and Mobic 15 mg Tablets (MEL1-11-01)

Pharmacokinetic Parameter	Least Squares Geometric Mean		GMR ^a	90% CI
	Vivlodex Capsules 12 mg Fasted	Mobic 15 mg Tablets Fasted		
C _{max} (ng/mL)	1536.6	1202.0	1.28	1.19, 1.37
AUC _{0-t} (hour*ng/mL)	32242.9	37381.3	0.86	0.84, 0.89
AUC _{0-∞} (hour*ng/mL)	37076.8	43559.8	0.85	0.82, 0.88

Data source: 5.3.1.2 MEL1-11-01 CSR, Table 14.2.3.

Abbreviations: AUC_{0-∞} = area under the concentration time curve from time 0 extrapolated to infinity; AUC_{0-t} = area under the concentration time curve from time 0 to the time of the last sample with a quantifiable concentration; CI = confidence interval; C_{max} = maximum plasma concentration; GMR = ratio of the geometric means

^a GMR is the ratio of least squares geometric means for Vivlodex Capsules 12 mg Fasted to Mobic 15 mg tablets Fasted.

2.7.2.2.3.2 Dose Proportionality

Administration of 6 mg and 12 mg doses of Vivlodex Capsules under fasted conditions resulted in dose-proportional meloxicam AUC_{0-t} and AUC_{0-∞}. The dose-normalized GMR for the comparison of meloxicam AUC_{0-t} and AUC_{0-∞} for Vivlodex Capsules 6 mg and 12 mg were both close to 1 and the 90% CIs around the GMRs were within the 0.8 to 1.25 equivalence limits. Similar results were observed for the comparison of the dose-normalized geometric means for meloxicam C_{max} for the 6 and 12 mg doses (5.3.1.2 MEL1-11-01 CSR, Table 14.2.4).

2.7.2.2.3.3 Food Effect

Administration of Vivlodex Capsules 12 mg under fed conditions decreased the rate of meloxicam absorption (C_{max}). The GMR (90% CI) of meloxicam C_{max} for Vivlodex Capsules 12 mg following a high fat meal compared with Vivlodex Capsules 12 mg in fasted conditions was 0.74 (0.69, 0.80), corresponding to approximately a 25% reduction in meloxicam C_{max} for fed subjects compared with fasted subjects (5.3.1.2 MEL1-11-01 CSR, Table 14.2.5). The 90% CI for the C_{max} comparison was below the 0.8 to 1.25 equivalence limits, indicating a significant difference in maximum plasma concentration following administration with food. In contrast to the reduced C_{max} demonstrated for Vivlodex Capsules 12 mg following a high fat meal, the Mobic 15 mg tablets C_{max} increased by approximately 11% following a high fat meal, and the GMR was within the 0.8 to 1.25 bioequivalence limits.

Consistent with the MEL1-12-04 trial, the median meloxicam t_{max} was delayed by approximately 3 hours following Vivlodex Capsules 12 mg administration under fed conditions compared with fasted conditions. The median meloxicam t_{max} for the Mobic 15 mg tablet group was delayed by 2 hours under fed conditions compared with fasted conditions.

Administration of Vivlodex Capsules 12 mg with food did not result in an appreciable decrease in the overall extent of exposure (AUC); the GMRs (90% CI) for meloxicam AUC_{0-t} and $AUC_{0-\infty}$ were 0.96 (0.92, 1.00) and 0.96 (0.92, 1.01), respectively, both within the 0.8 to 1.25 equivalence limits, indicating that the overall extent of exposure to meloxicam from Vivlodex Capsules 12 mg was statistically equivalent in fed and fasted subjects. Similar results were obtained for the evaluation of a food effect on overall extent of exposure following administration of Mobic 15 mg tablets.

Results of the statistical analysis of food effect for Vivlodex Capsules 12 mg in fed and fasted subjects, including the GMR and corresponding 90% CIs, are presented in Table 2.7.2.2.3.3-1. Mean meloxicam plasma concentrations over time for Vivlodex Capsules 12 mg under fed and fasted conditions are presented in Figure 2.7.2.2.3.3-1.

Results of the statistical analysis of food effect for Mobic tablets 15 mg in fed and fasted subjects, including the GMR and corresponding 90% CIs, are presented in Table 2.7.2.2.3.3-2.

Table 2.7.2.2.3.3-1 Statistical Analysis of Food Effect for Meloxicam Plasma Pharmacokinetic Parameters – Vivlodex Capsules 12 mg in Fasted and Fed Subjects (MEL1-11-01)

Pharmacokinetic Parameter	Least Square Geometric Mean		GMR ^a	90% CI
	Vivlodex Capsules 12 mg Fasted	Vivlodex Capsules 12 mg Fed		
C_{max} (ng/mL)	1515.7	1124.8	0.74	0.69, 0.80
AUC_{0-t} (hour*ng/mL)	32032.4	30818.1	0.96	0.92, 1.00
$AUC_{0-\infty}$ (hour*ng/mL)	36792.6	35376.1	0.96	0.92, 1.01
t_{max} (hour) ^b	1.97	5.00	3.26	2.76, 4.00

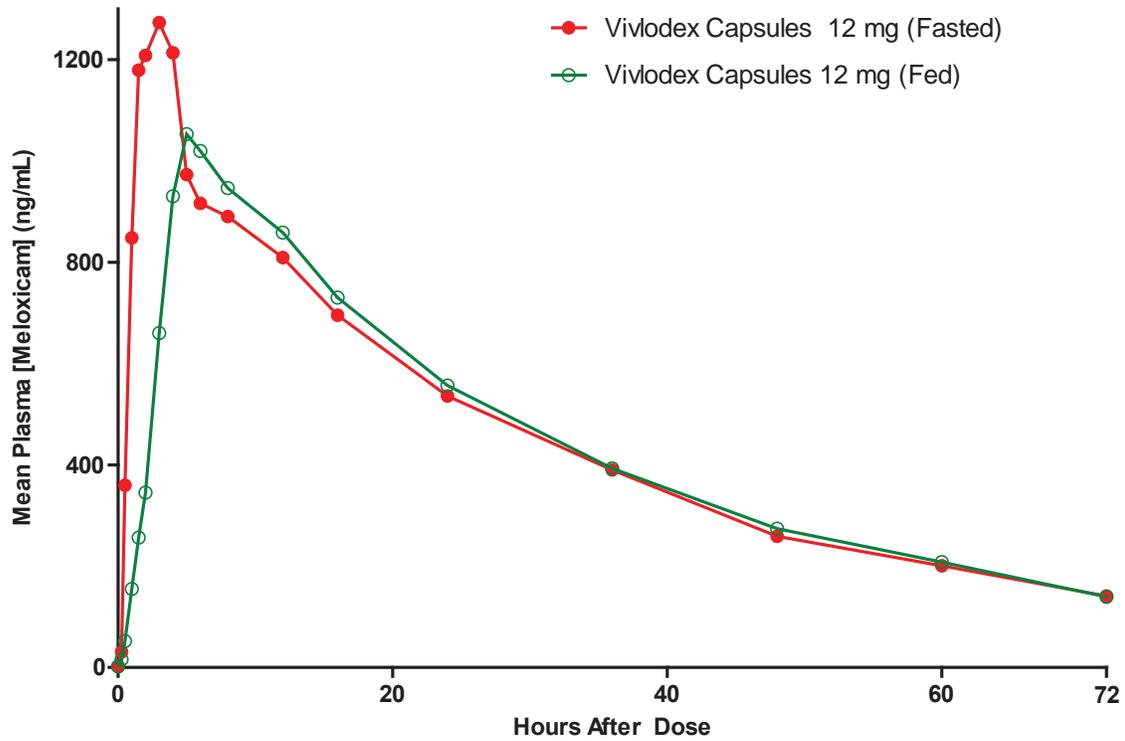
Data source: 5.3.1.2 MEL1-11-01 CSR, Table 14.2.5.

Abbreviations: $AUC_{0-\infty}$ = area under the concentration time curve from time 0 extrapolated to infinity; AUC_{0-t} = area under the concentration time curve from time 0 to the time of the last sample with a quantifiable concentration; CI = confidence interval; C_{max} = maximum plasma concentration; GMR = ratio of the geometric means; t_{max} = time to achieve maximum concentration

^a GMR is for Vivlodex Capsules 12 mg Fasted to Vivlodex Capsules 12 mg Fed.

^b Median values are provided for t_{max} .

Figure 2.7.2.2.3.3-1 Mean Plasma Meloxicam Concentrations in Fasted and Fed Subjects Following Administration of Vivlodex Capsules 12 mg (MEL1-11-01)



Data source: 5.3.1.2 MEL1-11-01 CSR, Table 14.2.1.

Table 2.7.2.2.3.3-2 Statistical Analysis of Food Effect for Meloxicam Plasma Pharmacokinetic Parameters – Mobic 15 mg Tablets in Fasted and Fed Subjects (MEL1-11-01)

Pharmacokinetic Parameter	Least Square Geometric Mean		GMR ^a	90% CI
	Mobic 15 mg Tablets Fasted	Mobic 15 mg Tablets Fed		
Mean C _{max} (ng/mL)	1192.5	1331.4	1.12	1.04, 1.20
Mean AUC _{0-t} (hour*ng/mL)	37362.7	38344.8	1.03	1.00, 1.06
Mean AUC _{0-∞} (hour*ng/mL)	43575.9	44859.2	1.03	0.99, 1.07
Median t _{max} (hour) ^b	4.02	6.00	0.48	-1.56, -1.5

Data source: 5.3.1.2 MEL1-11-01 CSR, Table 14.2.6.

Abbreviations: AUC_{0-∞} = area under the concentration time curve from time 0 extrapolated to infinity; AUC_{0-t} = area under the concentration time curve from time 0 to the time of the last sample with a quantifiable concentration; CI = confidence interval; C_{max} = maximum plasma concentration; GMR = ratio of the geometric means; t_{max} = time to achieve maximum concentration

^a GMR for the comparison of Mobic 15 mg tablets Fasted to Mobic 15 mg tablets Fed.

^b Median values are provided for t_{max}.

2.7.2.2.3.4 Conclusions

- Under fasted conditions, meloxicam C_{max} following Vivlodex Capsules 12 mg administration was higher than that of Mobic 15 mg tablets by approximately 28%.
- Overall systemic exposure to meloxicam following Vivlodex Capsules 12 mg administration was slightly less (<14%) than that of Mobic 15 mg tablets as measured by AUC_{0-t} and AUC_{0-∞} under fasted conditions. The GMRs (90% CI) for the comparisons of Vivlodex Capsules 12 mg and Mobic 15 mg tablets under fasted conditions were 0.86 (0.84 – 0.89) for AUC_{0-t} and 0.85 (0.82 – 0.88) for AUC_{0-∞}.
- Peak plasma concentrations occurred earlier for Vivlodex Capsules 12 mg (median t_{max}=1.97 hours) and 6 mg (median t_{max}=2 hours) than for Mobic 15 mg tablets (median t_{max}=4.02 hours) when administered to subjects under fasted conditions.
- Vivlodex Capsules 6 mg and 12 mg demonstrated dose proportional C_{max}, AUC_{0-t}, and AUC_{0-∞}.
- Overall systemic exposure (AUC) to meloxicam following administration of Vivlodex Capsules 12 mg under fasted or fed conditions was similar, as has been described for other NSAIDs. However, administration following a high-fat meal

decreased C_{\max} by approximately 25% and delayed t_{\max} by approximately 3 hours for Vivlodex Capsules 12 mg compared with fasted conditions.

- Overall systemic exposure (AUC) to meloxicam following administration of Mobic 15 mg tablets under fasted or fed conditions was similar. In contrast to the food effect observed for Vivlodex Capsules, Mobic 15 mg tablets demonstrated approximately an 11% increase in the meloxicam C_{\max} under fed conditions compared to fasted conditions. Although this effect was not statistically significant, the increase in C_{\max} following administration following a fat meal has been previously described for Mobic 15 mg tablets ([Mobic US PI, 2012](#)). Under fed conditions, the t_{\max} for Mobic 15 mg tablets was delayed by approximately 2 hours compared with fasted conditions, suggesting that administration with food influences the rate of absorption of meloxicam from Mobic tablets.

2.7.2.2.4 Clinical Trial QP09C03

Single-Dose, 4-Way Crossover, Relative Bioavailability Study of Meloxicam Nanoformulation 7.5 mg Capsules and Mobic® 7.5 mg Capsules in Healthy Subjects under Fed and Fasted Conditions

Clinical trial [QP09C03](#) was a non-IND study conducted in Australia by the previous sponsor. Mobic is sold in Australia as a capsule formation and not as a tablet; therefore, capsules were used in this trial. A total of 14 subjects received at least 1 dose of trial drug in this pilot study and were included in the full analysis set. Thirteen subjects completed all 4 trial periods, and 1 subject withdrew during Period 3. The population included more males (64.3%) than females (35.7%) with a mean age of 25.1 years, and ages ranging from 18.0 to 47.0 years. A tabular summary of the pharmacokinetic parameters is presented in [Table 2.7.2.2.4-1](#) and described in further detail in the sections that follow.

Table 2.7.2.2.4-1 Summary of the Meloxicam Pharmacokinetic Parameters (QP09C03)

Mean±SD	Vivlodex Capsules		Mobic Capsules	
	7.5 mg Fasted n=14	7.5 mg Fed n=14	7.5 mg Fasted n=14	7.5 mg Fed n=14
C _{max} (ng/L)	1087±222	878±203	628±149	736±131
t _{max} (hour) ^a	2.00	5.00	5.00	6.00
AUC _{0-t} (hour*ng/mL)	19157±6003	18591±4615	17200±4893	17902±5088
AUC _{0-∞} (hour*ng/mL)	24467±12855	27707±20402	25631±16818	25441±12881
λ _z (1/hour)	0.04±0.01	0.03±0.01	0.03±0.01	0.03±0.01
t _{1/2} (hour) ^b	19.49±7.70	24.89±18.39	24.48±15.46	24.61±15.93

Data source: 5.3.1.2 QP09C03 CSR, Table 2.1 and Table 2.2.

Abbreviations: λ_z = terminal elimination rate constant; AUC_{0-inf} = area under the concentration time curve from time 0 extrapolated to infinity; AUC_{0-t} = area under the concentration time curve from time 0 to the time of the last sample with a quantifiable concentration; C_{max} = maximum plasma concentration; Min = minimum; Max = maximum; SD = standard deviation; t_{1/2} = terminal elimination half-life; t_{max} = time to achieve maximum concentration

^a Median values were calculated for t_{max}.

^b The apparent differences in t_{1/2} of Vivlodex Capsules and Mobic capsules can be attributed to the influence of a single subject, who recorded higher than average elimination rates for meloxicam (t_{1/2} of Vivlodex Capsules = 42.03 hours; t_{1/2} of Mobic capsules = 74.25 hours). It was determined that this subject may be a poor metabolizer of meloxicam.

2.7.2.2.4.1 Rate and Extent of Absorption

The mean peak meloxicam plasma concentration (C_{max}) in subjects administered Vivlodex Capsules 7.5 mg under fasted conditions (1087±222 ng/mL) was 1.7-fold higher than in subjects administered Mobic capsules 7.5 mg (628±149 ng/mL) under fasted conditions. The GMR (90% CI) for the comparison of meloxicam C_{max} was above the upper equivalence limit of 1.25 (1.74 [1.60, 1.89]) indicating that Vivlodex Capsules 7.5 mg and Mobic capsules 7.5 mg did not have similar rates of meloxicam absorption under fasted conditions. Median meloxicam t_{max} occurred significantly earlier for Vivlodex Capsules 7.5 mg (2.00 hours) compared with Mobic capsules 7.5 mg (5.00 hours; P=0.002) (5.3.1.2 QP09C03 CSR).

The overall extent of exposure to meloxicam (AUC_{0-t} and AUC_{0-∞}) following administration of Vivlodex Capsules 7.5 mg dose was slightly higher than that observed for Mobic capsules 7.5 mg based on a comparison of AUC_{0-t}. The GMR (90% CI) for the comparison of AUC_{0-t} was 1.11 (1.07, 1.15). In contrast, the GMR (90% CI) for the comparison of AUC_{0-∞} was

0.99 (0.93, 1.06) and was within the 0.8 to 1.25 equivalence limits, suggesting comparable total systemic exposure from the two drug products (5.3.1.2 QP09C03 CSR).

Results of the statistical analysis of relative bioavailability of Vivlodex Capsules 7.5 mg and Mobic capsules 7.5 mg under fasted conditions, including GMRs with 90% CIs for the parameter comparisons, are summarized in Table 2.7.2.2.4-1. Mean plasma meloxicam concentrations over time under fasted and fed conditions are presented for the Vivlodex Capsules 7.5 mg and Mobic capsules 7.5 mg groups in Figure 2.7.2.2.4.1-1.

Table 2.7.2.2.4.1-1 Statistical Analysis of Relative Bioavailability in Fasted Subjects for Meloxicam Plasma Pharmacokinetic Parameters – Vivlodex Capsules 7.5 mg and Mobic Capsules 7.5 mg (QP09C03)

Pharmacokinetic Parameter	Least Squares Geometric Mean		GMR ^a	90% CI
	Vivlodex Capsules 7.5 mg Fasted	Mobic Capsules 7.5 mg Fasted		
C _{max} (ng/mL)	1064	612	1.74	1.60, 1.89
AUC _{0-t} (hour*ng/mL)	18397	16608	1.11	1.07, 1.15
AUC _{0-∞} (hour*ng/mL)	22399	22657	0.99	0.93, 1.06
t _{max} (hour) ^b	2.00	5.00	--	--

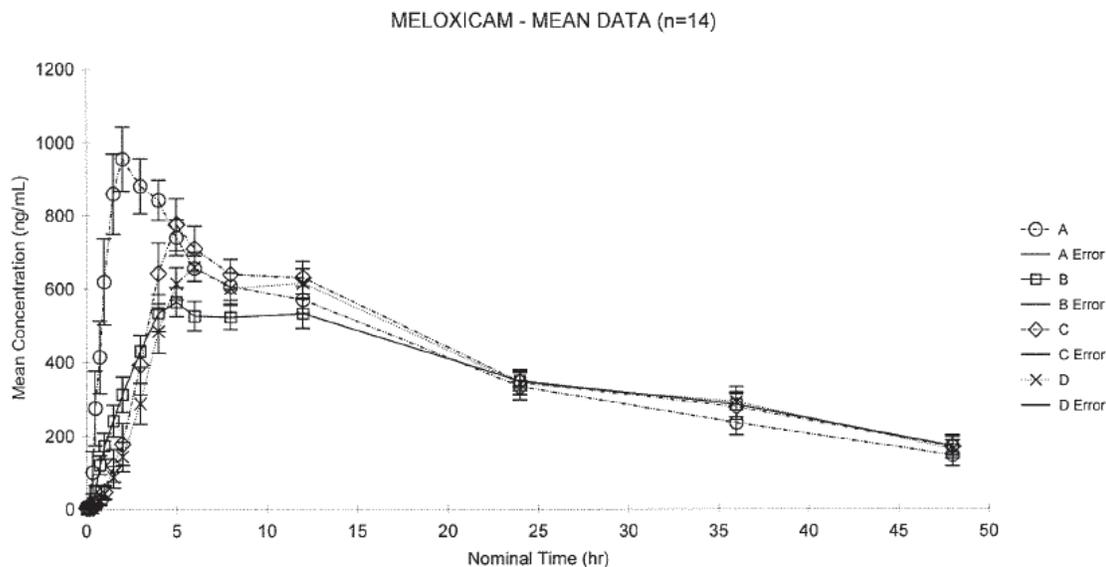
Data source: 5.3.1.2 QP09C03 CSR.

Abbreviations: AUC_{0-∞} = area under the concentration time curve from time 0 extrapolated to infinity; AUC_{0-t} = area under the concentration time curve from time 0 to the time of the last sample with a quantifiable concentration; CI = confidence interval; C_{max} = maximum plasma concentration; GMR = ratio of the geometric means

^a For AUC_{0-t}, AUC_{0-inf}, and C_{max}, the ratio is of least squares geometric means for Vivlodex Capsules 7.5 mg Fasted to Mobic capsules 7.5 mg Fasted. For t_{max}, the ratio is of the medians (Vivlodex Capsules 7.5 mg Fasted to Mobic capsules 7.5 mg Fasted).

^b Mean values are presented for t_{max}. Comparison of t_{max} between Vivlodex Capsule and Mobic capsules under fasted conditions was considered statistically significant (P=0.002) by Wilcoxon Test.

Figure 2.7.2.2.4.1-1 Mean Plasma Meloxicam Concentrations in Fasted and Fed Subjects Following Administration of Vivlodex Capsules 7.5 mg and Mobic capsules 7.5 mg (QP09C03)



A = Test Product: Fasted conditions; B= Reference Product: Fasted conditions; C = Test Product: Fed conditions; D= Reference Product: Fed conditions

Data source: 5.3.1.2 QP09C03 CSR, Figure 11.1.

2.7.2.2.4.2 Food Effect

Similar to the food effect described in trials MEL1-11-01 and MEL1-12-04, administration of Vivlodex Capsules 7.5 mg under fed conditions resulted in decreased rate of meloxicam absorption (C_{max}). The mean meloxicam C_{max} in subjects administered Vivlodex Capsules 7.5 mg under fed conditions (878 ± 203 ng/mL) was 20% lower compared with fasted conditions; however, under fed conditions, the observed C_{max} of Vivlodex Capsules 7.5 mg was still numerically higher than that of Mobic capsules 7.5 mg (736 ± 131 ng/mL). The GMR (90% CI) for the comparison of Vivlodex Capsules 7.5 mg and Mobic capsules 7.5 mg C_{max} was 1.18 (1.08, 1.28). The upper bound of the 90% CI was slightly higher than the upper equivalence limit, indicating a marginal difference in the C_{max} of Vivlodex Capsules 7.5 mg under fed conditions compared with that for Mobic capsules 7.5 mg.

Under fed conditions, the median t_{max} following administration of Vivlodex Capsules 7.5 mg and Mobic capsules 7.5 mg was delayed by approximately 3 hours ($t_{max}=5.00$ hours) and 1 hour ($t_{max}=6.00$ hours), respectively, compared with fasted subjects.

The overall extent of exposure to meloxicam (AUC_{0-t} and $AUC_{0-\infty}$) following administration of Vivlodex Capsules 7.5 mg with food was comparable to that of Mobic capsules 7.5 mg, as demonstrated by the 90% CIs around the GMRs for the comparisons of AUC_{0-t} (1.01, 1.09) and $AUC_{0-\infty}$ (0.97, 1.11).

Results of the statistical analysis of relative bioavailability for Vivlodex Capsules 7.5 mg and Mobic capsules 7.5 mg in fed subjects, including GMRs and corresponding 90% CIs, are presented in Table 2.7.2.2.4.2-1.

Table 2.7.2.2.4.2-1 Statistical Analysis of Relative Bioavailability for Meloxicam Plasma Pharmacokinetic Parameters – Vivlodex Capsules 7.5 mg and Mobic capsules 7.5 mg in Fed Subjects (QP09C03)

Pharmacokinetic Parameter	Least Squares Geometric Mean		GMR ^a	90% CI
	Vivlodex Capsules 7.5 mg Fed	Mobic Capsules 7.5 mg Fed		
C _{max} (ng/mL)	859	726	1.18	1.08, 1.28
AUC _{0-t} (hour*ng/mL)	18097	17307	1.05	1.01, 1.09
AUC _{0-∞} (hour*ng/mL)	24122	23118	1.04	0.97, 1.11
t _{max} (hour) ^b	5.00	6.00	--	--

Data source: 5.3.1.2 QP09C03 CSR.

Abbreviations: AUC_{0-∞} = area under the concentration time curve from time 0 extrapolated to infinity; AUC_{0-t} = area under the concentration time curve from time 0 to the time of the last sample with a quantifiable concentration; CI = confidence interval; C_{max} = maximum plasma concentration; t_{max} = time to achieve maximum concentration

^a GMR for the comparison of Vivlodex Capsules 7.5 mg Fed to Mobic tablets 15 mg Fed.

^b Median values are presented for t_{max}.

2.7.2.2.4.3 Conclusions

- Under fasted conditions, meloxicam C_{max} of Vivlodex Capsules 7.5 mg was 1.7-fold higher compared with the C_{max} of Mobic capsules 7.5 mg. The GMR (90% CI) for the comparison of Vivlodex C_{max} and meloxicam C_{max} was 1.74 (1.60, 1.89), which was above the upper bioequivalence acceptance limit of 1.25, indicating higher absorption of meloxicam from Vivlodex Capsules 7.5 mg. Under fed conditions, the meloxicam C_{max} following Vivlodex Capsules 7.5 mg administration was reduced compared to fasted conditions, but it was still higher than that of Mobic capsules 7.5 mg under fed conditions, with the upper bound of the 90% CI (1.08, 1.28) marginally above the bioequivalence acceptance limit.
- The overall extent of meloxicam exposure under fasted and fed conditions (AUC_{0-t} and AUC_{0-∞}) from Vivlodex Capsules 7.5 mg was biologically equivalent to that of Mobic capsules 7.5 mg.
- The time to achieve maximum meloxicam concentration (t_{max}) was significantly faster following administration of Vivlodex Capsules 7.5 mg compared with

Mobic capsules 7.5 mg under fasted conditions. Following a high-fat meal, the meloxicam t_{max} for subjects administered Vivlodex Capsules 7.5 mg and Mobic capsules 7.5 mg were delayed by 3 hours and 1 hour, respectively.

2.7.2.3 Comparison and Analyses of Results Across Vivlodex Capsules Trials

Vivlodex Capsules are a new meloxicam drug product under development by Iroko for the management of OA pain which utilize SoluMatrix technology to considerably reduce the drug substance particle size and, in turn, increase the drug particle surface area. Phase 1 trials ([MEL1-11-01](#) and [MEL1-12-04](#)) were conducted to test the hypothesis that the increased drug particle surface area would enhance the rates of dissolution and absorption of meloxicam. It is postulated that the enhanced pharmacokinetic profile could result in a more rapid onset of pain relief and satisfactory efficacy at lower doses than are found in currently available meloxicam drug products such as Mobic tablets.

The Pilot PK Trial ([QP09C03](#)) using the Pilot Formulation of Vivlodex Capsules was conducted in Australia. A 7.5 mg Vivlodex Capsules dose strength was evaluated in a crossover fashion against Mobic 7.5 mg capsules in healthy subjects under fasted and fed conditions. The pharmacokinetic data indicated that the application of SoluMatrix technology achieved the desired effect of increasing meloxicam absorption from Vivlodex Capsules compared to that from Mobic, supporting the rationale that a low-dose meloxicam formulation with enhanced absorption kinetics warranted further development. iCeutica (the former Sponsor of the study) subsequently formulated a 6 mg dosage strength capsule (ie, 20% dose reduction) using the same formulation and process used for formulating the pilot 7.5 mg dosage strength capsule.

The Initial PK Trial ([MEL1-11-01](#)) using the POC Formulation of Vivlodex Capsules evaluated 6 mg and 12 mg dosage strengths in a crossover trial against Mobic 15 mg tablets in fasted and fed healthy subjects (6 mg Vivlodex Capsules fasted only). Results from this trial are explained in detail in [Section 2.7.2.2.3](#) and the following sections. In brief, the C_{max} of Vivlodex Capsules was >25% higher and the $AUC_{0-\infty}$ was approximately 15% lower compared with those of the reference product Mobic in the fasted state. Following completion of this trial, Vivlodex Capsules containing 5 and 10 mg were selected for further development.

Population PK modeling and simulation were subsequently performed ([Meloxicam Population PK Analysis Report](#)) and confirmed that 5 mg and 10 mg Vivlodex dose strengths would likely meet the target product PK profile of comparable C_{max} and >20% reduction in AUC compared with Mobic 7.5 mg and 15 mg tablets, respectively. As a result, Vivlodex Capsules containing 5 mg and 10 mg of meloxicam were produced using a commercial-scale manufacturing process for further clinical evaluation. The 5 mg and 10 mg Vivlodex capsules (Commercial Formulation) were evaluated in a Definitive Phase 1 PK Trial ([MEL1-12-04](#)), in the Pivotal Phase 3 Trial ([MEL3-12-02](#)) in patients with OA pain, and in an open-label safety trial ([MEL3-12-03](#)). Trials [MEL3-12-02](#) and [MEL3-12-03](#) are

summarized in detail in [2.7.3 Summary of Clinical Efficacy](#) and [2.7.4 Summary of Clinical Safety](#).

The Definitive Phase 1 Trial ([MEL1-12-04](#)) used a similar crossover trial design as [MEL1-11-01](#), and evaluated the pharmacokinetic characteristics of 5 mg and 10 mg dosage strengths of the Commercial Formulation of Vivlodex Capsules in fasted and fed subjects compared with Mobic 15 mg tablets. The results from this trial are discussed in [Section 2.7.2.2.2](#) and the following sections. In brief, this trial confirmed that the fasting meloxicam C_{\max} following administration of a 10 mg dose of Vivlodex Capsules was comparable with the fasting C_{\max} value following Mobic 15 mg tablet administration, with a significantly reduced $AUC_{0-\infty}$. A tabular summary of the pharmacokinetic results for clinical trials MEL1-12-04 and MEL1-11-01 is presented in [Table 2.7.2.3-1](#) and described in further detail in the sections that follow.

2.7.2.3.1 Rate and Extent of Absorption

In the 3 Phase 1 trials, Vivlodex Capsules demonstrated a more rapid absorption phase compared with the reference Mobic product. Under fasted conditions, the median times to achieving peak meloxicam plasma concentration (t_{\max}) were consistently 50% lower for Vivlodex Capsules, reflecting absorption of meloxicam that was significantly faster for Vivlodex Capsules than for Mobic tablets in all 3 trials. In trial MEL1-12-04, the mean peak plasma meloxicam concentration (C_{\max}) following administration of Vivlodex Capsules 10 mg was comparable with that of Mobic 15 mg tablets under fasted conditions. Notably, less variability was also observed for C_{\max} with Vivlodex Capsules 10 mg. In the remaining 2 trials, the meloxicam C_{\max} was found to be increased following administration of Vivlodex Capsules compared with Mobic tablets under fasted conditions. Taken together, the results from these trials show that, under fasted conditions and in comparison to Mobic 15 mg tablets, Vivlodex Capsules demonstrate the following:

- Similar or slightly elevated C_{\max}
- Earlier t_{\max}
- Lower overall extent of exposure ($AUC_{0-\infty}$)

Low variability was present in C_{\max} values for Vivlodex Capsules 10 mg, as demonstrated by the small SD (Table 2.7.2.3-1) relative to that observed for Mobic 15 mg tablets. In trial MEL1-11-01, the mean meloxicam C_{\max} values in fasted subjects were higher for Vivlodex Capsules 12 mg (1541.9 ng/mL) and slightly decreased for Mobic 15 mg tablets (1199.6 ng/mL) than those observed in trial MEL1-12-04. In trial MEL1-12-04, the range of meloxicam C_{\max} values achieved by individual subjects administered Vivlodex Capsules 10 mg and Mobic 15 mg tablets overlapped considerably (with the exception of Subject 15) (Table 2.7.2.3-1). In contrast, there was less overlap in meloxicam C_{\max} values in individual subjects following administration of Vivlodex Capsules 12 mg compared with the C_{\max} values achieved with Mobic 15 mg tablets administration in trial MEL1-11-01. Notably, the median t_{\max} values following administration of Vivlodex Capsules 10 mg (MEL1-12-04) and 12 mg (MEL1-11-01) were similar, and occurred 2 hours earlier compared with Mobic 15 mg tablets.

The overall extent of meloxicam absorption as assessed by $AUC_{0-\infty}$ was approximately 14% (MEL1-11-01) to 33% (MEL1-12-04) lower for Vivlodex Capsules 12 mg and 10 mg, respectively, compared with Mobic 15 mg tablets under fasted conditions. The GMR and 90% CI for the comparison of meloxicam $AUC_{0-\infty}$ following Vivlodex Capsules 12 mg and Mobic 15mg tablet administration were within the 0.8 to 1.25 bioequivalence limits in trial MEL1-11-01. As expected, the GMR (90% CI) for the comparison of Vivlodex Capsules 10 mg and Mobic 15 mg tablets was considerably lower at 0.67 (0.64, 0.71) for $AUC_{0-\infty}$ in trial MEL1-12-04. Results based on AUC_{0-t} were similar to that observed with $AUC_{0-\infty}$. Both the rate and extent of absorption observed in trial MEL1-12-04 confirm the results of the [Meloxicam Population PK Analysis Report](#) that modeled the expected pharmacokinetic properties of 5 and 10 mg doses of Vivlodex Capsules based on data from the first 2 Phase 1 trials.

In all 3 Phase 1 trials, the meloxicam t_{\max} following administration of Vivlodex Capsules under fasted conditions was around 2 hours (regardless of dosages) and occurred 2 to 3 hours earlier than for Mobic tablets (Table 2.7.2.3-1).

2.7.2.3.2 Dose Proportionality

In both the MEL1-12-04 and the MEL1-11-01 trials, the dosages of Vivlodex Capsules demonstrated linear meloxicam pharmacokinetic characteristics and dose proportionality between 5 mg and 10 mg (MEL1-12-04) and 6 mg and 12 mg (MEL1-11-01) for C_{\max} , AUC_{0-t} and $AUC_{0-\infty}$ (Table 2.7.2.3-1).

2.7.2.3.3 Food Effect

Consistently across trials, administration with food resulted in a reduction in the rate of meloxicam absorption from Vivlodex Capsules (C_{\max} and t_{\max}). Meloxicam absorption from Vivlodex Capsules 10 mg and 12 mg (C_{\max}) was decreased by approximately 22% (MEL1-12-04) and 25% (MEL1-11-01), and t_{\max} was delayed by approximately 3 hours under fed conditions. Similar effects of food on meloxicam absorption were observed for Vivlodex Capsules 7.5 mg in trial QP09C03. In contrast to Vivlodex Capsules, administration of Mobic tablets with food led to an increase in the meloxicam C_{\max} values compared with fasted conditions.

The overall extent of meloxicam exposure from Vivlodex Capsules was generally unaffected by food (appreciable decreases in $AUC_{0-\infty}$ and AUC_{0-t} were not observed). These results are consistent with those observed following administration of other NSAIDs with food (Verbeeck RK et al, 1983).

2.7.2.3.4 Conclusions Across Studies

- The mean meloxicam C_{\max} was slightly elevated following administration of Vivlodex Capsules 12 mg and similar for Vivlodex Capsules 10 mg compared with the C_{\max} of Mobic 15 mg tablets under fasted conditions.
- Across all 3 trials, the median t_{\max} occurred earlier for Vivlodex Capsules (2 hours) than for Mobic tablets (4 to 5 hours).
- The overall extent of meloxicam exposure was lower for Vivlodex Capsules 12 mg and 10 mg compared with Mobic 15 mg tablets.
- As described for other NSAIDs, administration of Vivlodex Capsules under fed conditions decreased the rate (C_{\max} and t_{\max}) but not the overall extent of meloxicam absorption (AUC_{0-t} and $AUC_{0-\infty}$).
- Vivlodex Capsules administration was associated with dose proportional pharmacokinetics for both the 6 mg and 12 mg dosages and the 5 mg and 10 mg dosages.
- The pharmacokinetic characteristics of Vivlodex Capsules were generally consistent across the 3 Phase 1 trials across the range of dose strengths tested.

2.7.2.4 Comparison and Analyses of Results Across Published Meloxicam Studies and FDA Approved Meloxicam Prescribing Information

Vivlodex Capsules are being filed as a 505(b)(2) NDA. The application relies on results from Vivlodex Capsules clinical trials and is supported by previous pharmacokinetic, efficacy, and safety findings for meloxicam capsules. Meloxicam is available as a suspension or in oral capsule/tablet form and can be administered by IV and intramuscular (IM) injections, rectal suppositories, and oral capsules/tablets (Davies NM and Skjodt NM, 1999). Because Vivlodex Capsules are intended for oral administration, the pharmacokinetic (PK) and pharmacodynamic (PD) characteristics summarized will focus on orally administered meloxicam products. Mobic (meloxicam) 15 mg tablets were chosen as the appropriate reference product for Vivlodex Capsules. Trials QP09C03, MEL1-11-01, and MEL1-12-04 determined the relative bioavailability of Vivlodex Capsules and Mobic tablets. In these trials, the rate (C_{max} and t_{max}) of meloxicam absorption from Vivlodex Capsules was enhanced relative to the known rate of meloxicam absorption following Mobic administration. As expected, the overall extent of meloxicam exposure (as measured by $AUC_{0-\infty}$ and AUC_{0-t}) was lower following Vivlodex Capsules administration compared with Mobic tablets administration (Mobic US PI, 2012).

Following absorption of meloxicam from Vivlodex Capsules, it is expected that the known PK and PD characteristics of meloxicam will also apply to meloxicam derived from Vivlodex Capsules. Vivlodex Capsules have demonstrated efficacy with the potential for improved tolerability compared with Mobic tablets due to the enhanced rate of absorption and lower overall extent of exposure, respectively. In this section, relevant PK and PD findings from the Mobic tablets Prescribing Information and published literature are highlighted.

2.7.2.4.1.1 Absorption

According to the Mobic US PI, meloxicam attains peak plasma concentrations at approximately 4 to 5 hours following single oral doses of Mobic 7.5 mg under fasted conditions, indicating prolonged drug absorption. Other reports indicate that maximum plasma concentrations (ie, C_{max}) occurred 9 to 11 hours following oral administration of a 30 mg Mobic capsule (Davies NM and Skjodt NM, 1999). Orally administered Mobic tablets 30 mg are approximately 89% bioavailable compared with a 30 mg IV bolus injection (Mobic US PI, 2012). Following single IV doses, dose-proportional meloxicam pharmacokinetics were shown in the range of 5 mg to 60 mg. Following multiple oral doses, meloxicam demonstrated dose-proportional pharmacokinetics over the range of 7.5 mg to 15 mg (Mobic US PI, 2012).

The peak plasma meloxicam concentration is increased by approximately 22% when Mobic tablets are taken with food; (b) (4) (Mobic US PI, 2012). The overall bioavailability (ie, overall extent of exposure) of meloxicam is not influenced by food (Mobic US PI, 2012). In contrast to Mobic tablets, food decreased the rate (C_{max} and t_{max}) of meloxicam absorption following administration of

Vivlodex Capsules; however, the overall extent of meloxicam absorption ($AUC_{0-\infty}$) from Vivlodex Capsules 10 mg was not affected.

2.7.2.4.1.2 Distribution and Plasma Protein Binding

Meloxicam is highly bound to serum albumin (about 99.4%) over the expected range of therapeutic plasma concentrations (Mobic US PI, 2012). Meloxicam tissue distribution is similar to other oxicams, and meloxicam readily penetrates into perivascular spaces, including the synovial fluid (Davies NM and Skjodt NM, 1999). Following a 60 mg oral loading dose and subsequent 30 mg oral doses, synovial fluid concentrations of meloxicam were 40% to 60% of the meloxicam plasma concentrations (Davies NM and Skjodt NM, 1999). The free fraction in synovial fluid is 2.5 times higher than in plasma, due to the lower albumin content in synovial fluid as compared to plasma. The significance of synovial fluid penetration is unknown (Mobic US PI, 2012).

In vivo studies found that meloxicam crosses the blood-brain barrier. Following rapid carotid infusion into rats, 19% of administered radiolabelled meloxicam was recovered from brain homogenates 5 seconds following the injection. Intracellular meloxicam accounted for 23% of the total measured radioactivity (Jolliet P et al, 1997; Davies NM and Skjodt NM, 1999). Meloxicam penetration into human red blood cells following oral dosing is less than 10%. Following a radiolabeled dose, over 90% of the radioactivity detected in the plasma was present as unchanged meloxicam (Mobic US PI, 2012).

Similar protein binding characteristics and distribution are expected for Vivlodex Capsules.

2.7.2.4.1.3 Metabolism

Meloxicam is extensively metabolized in the liver to 4 pharmacologically inactive metabolites. Meloxicam metabolites include 5'-carboxy meloxicam (60% of dose), from P450-mediated metabolism formed by oxidation of an intermediate metabolite 5'-hydroxymethyl meloxicam which is also excreted to a lesser extent (9% of dose). In vitro studies indicate that CYP2C9 plays an important role in this metabolic pathway with a minor contribution of the CYP3A4 isozyme. Peroxidase activity is probably responsible for the other 2 metabolites which account for 16% and 4% of the administered dose, respectively (Davies NM and Skjodt NM, 1999; Mobic US PI, 2012).

A similar metabolic pathway is expected for Vivlodex Capsules.

2.7.2.4.1.4 Excretion

Meloxicam excretion is predominantly in the form of metabolites, eliminated via renal, biliary, and fecal excretion. The unchanged parent compound is found in only trace amounts in the urine (0.2%) and feces (1.6%) (Mobic US PI, 2012, Davies NM and Skjodt NM, 1999). The 4 metabolites of meloxicam in urine account for 42.8% of an administered radioactive meloxicam dose (Chesne C, et al, 1998). Fecal and urinary metabolite distributions differed significantly. One of the metabolites comprised approximately 98% of fecal metabolites, with only traces of the remaining 3 metabolites being detected (Chesne C, et al, 1998; Davies NM and Skjodt NM, 1999). The mean half-life ($t_{1/2}$) of meloxicam is

estimated to be approximately 15-20 hours (Mobic US PI, 2012; Türck D et al, 1996). In Phase 1 trials, the $t_{1/2}$ for Vivlodex Capsules was found to be within this range.

Similar excretion characteristics are expected for Vivlodex Capsules.

2.7.2.4.1.5 Effect of Dose on Key Pharmacokinetic Parameters

Meloxicam demonstrates proportional increases in C_{max} and AUC with increases in dosage within the range of 7.5 mg to 30 mg (Davies NM and Skjodt NM, 1999; Türck D et al, 1996). Dose proportionality was similarly demonstrated for the Vivlodex Capsules 6 mg and 12 mg (MEL1-11-01) as well as 5 mg and 10 mg doses (MEL1-12-04) in Vivlodex Capsules clinical trials (Section 2.7.2.3.2).

2.7.2.4.1.6 Single-Dose and Multiple-Dose Pharmacokinetics

The Mobic PI indicates that the pharmacokinetics of meloxicam capsules were dose-proportional over the range of 7.5 mg to 15 mg and that, with multiple dosing, steady state concentrations were reached by Day 5. The multiple dose pharmacokinetics of Vivlodex Capsules 5 mg and 10 mg were not studied in the Phase 1 QP09C03, MEL1-11-01 and MEL1-12-04 trials. Although meloxicam has a $t_{1/2}$ of 15 to 20 hours, accumulation of meloxicam is not expected.

2.7.2.4.1.7 Drug-Demographic Interactions

2.7.2.4.1.7.1 EFFECTS OF AGE

The FDA standard NSAID Package Insert Labeling Template includes a warning that elderly patients may be at greater risk for serious GI events, including ulceration, bleeding, and perforation (FDA Proposed NSAID Package Insert Labeling Template 1). Meloxicam pharmacokinetics have been studied in pediatric (>2 years of age) and geriatric patients, in addition to healthy adults. In pediatric studies, there was a trend of approximately 30% lower exposure in younger patients (2 to 6 years of age) compared with the older patients (7 to 16 years of age) following single-dose administration after achieving a steady-state. The mean meloxicam $t_{1/2}$ (15.2 hours) was slightly higher in younger patients compared with older patients ($t_{1/2}$ =13.0 hours). However, in a covariate analysis using population pharmacokinetics, it was found that body-weight, but not age, was the single predictive covariate of meloxicam oral plasma clearance (Mobic US PI, 2012). Meloxicam pharmacokinetic properties have not been studied in patients <2 years of age.

Studies in older subjects found that males ≥ 65 years of age demonstrated meloxicam plasma concentration and steady-state pharmacokinetics similar to younger males. Females ≥ 65 years of age have been shown to demonstrate a 47% higher AUC and 32% higher C_{max} compared with younger females (≤ 55 years of age), but the AE profile for elderly females was similar to elderly males (Mobic US PI, 2012, Davies NM and Skjodt NM, 1999). Additionally, the incidence of AEs in elderly females was not higher than in younger females following meloxicam administration (Türck D et al, 1996). A population pharmacokinetic analysis that included data from RA patients in 3 clinical trials, concluded that age was a significant factor in meloxicam clearance. Older patients demonstrated decreased clearance

of meloxicam compared with younger patients ($P < 0.005$) (Meineke I and Türck D, 2003). Taken together, these studies indicate that advanced age affects C_{max} , AUC, and meloxicam clearance.

The Phase 1 trials of Vivlodex Capsules studied younger populations (<55 years of age); consequently an age effect could not be determined. Administration of Vivlodex Capsules is expected to show a similar age effect as Mobic tablets; however, because of the reduced meloxicam exposure demonstrated for Vivlodex Capsules the overall effect of age on pharmacokinetics and safety may be reduced.

2.7.2.4.1.7.2 EFFECTS OF GENDER

The Mobic PI describes a gender effect on the pharmacokinetic properties of orally administered meloxicam (Mobic US PI, 2012). Young females exhibit slightly lower plasma concentration of meloxicam than young males. Following a single dose of Mobic 7.5 mg tablets, the mean meloxicam elimination $t_{1/2}$ in females was 19.5 hours compared with 23.4 hours for males. The data were similar at steady state (17.9 hours for females; 21.4 hours for males) (Mobic US PI, 2012). According to the Mobic PI, this pharmacokinetic difference is likely to be of little clinical importance because the pharmacokinetics demonstrate linearity and no difference in C_{max} or t_{max} was observed between genders. Much of the published literature does not describe a gender effect with meloxicam use (5.4 Literature References); however, in a population pharmacokinetic analysis, female gender was found to be significantly associated with decreased meloxicam clearance (Meineke I and Türck D, 2003).

Phase 1 trials of Vivlodex Capsules included slightly more male subjects than female subjects; however, subgroup analyses by gender were not performed. The published literature and clinical trials indicate that there is a gender effect on meloxicam pharmacokinetics.

2.7.2.4.1.7.3 EFFECTS OF RACE AND ETHNICITY

There are no statements in the Mobic PI that describe differences in pharmacokinetics, efficacy, or tolerability related to race or ethnicity. A review of the published literature did not reveal any evidence of an impact of race or ethnicity on meloxicam pharmacokinetic properties.

2.7.2.4.1.8 Drug-Drug Interaction Clinical Trials

Drug interactions related to concomitant use of meloxicam have been previously characterized (Mobic US PI, 2012; Türck D et al, 1996; Davies NM and Skjodt NM, 1999). Class labeling for NSAIDs includes precautions regarding the concomitant use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin II antagonists, aspirin, beta-adrenoceptor blocking agents, furosemide, cyclosporine, diflunisal, digoxin, diuretics, lithium, methotrexate, probenecid, and anticoagulants. The effects of anticoagulants such as warfarin and NSAIDs on GI bleeding are synergistic, such that there is a higher risk of serious GI bleeding in users of both drugs compared with use of either drug alone.

According to the Mobic PI and the published literature, the pharmacokinetic properties of both meloxicam and the following drugs showed no significant changes with concomitant use: cimetidine, digoxin, furosemide, antacids, and methotrexate (Mobic US PI, 2012; Türk D et al, 1996; Davies NM and Skjodt NM, 1999). Drug-drug interactions of note are listed below:

- Aspirin: When Mobic is administered with aspirin (1000 mg three times daily) to healthy volunteers, an increase in the AUC (10%) and C_{max} (24%) of meloxicam was noted (Mobic US PI, 2012). The clinical significance of this interaction is not known; however, as with other NSAIDs concomitant administration of meloxicam and aspirin is not generally recommended because of the potential for increased adverse effects (Mobic US PI, 2012; Davies NM and Skjodt NM, 1999).
- Lithium: In a trial conducted in healthy subjects, mean predose lithium concentration and AUC were increased by 21% in subjects receiving lithium doses ranging from 804 to 1072 mg twice daily with meloxicam 15 mg once daily as compared to subjects receiving lithium alone. These effects have been attributed to inhibition of renal prostaglandin synthesis by Mobic. It is recommended that patients on lithium treatment be closely monitored when Mobic is introduced, adjusted, or withdrawn (Mobic US PI, 2012).
- Cholestyramine: Healthy male volunteers were administered oral cholestyramine resin 3 times daily and IV meloxicam 15 mg. Pretreatment for 4 days with cholestyramine significantly increased the clearance of meloxicam by 50%. This resulted in a decrease in $t_{1/2}$, from 19.2 hours to 12.5 hours, and a 35% reduction in AUC. This suggests the existence of a recirculation pathway for meloxicam in the GI tract. The clinical relevance of this interaction has not been established (Mobic US PI, 2012; Davies NM and Skjodt NM, 1999).
- Warfarin: Studies evaluating the interaction between meloxicam and warfarin have shown that meloxicam does not appreciably affect the pharmacokinetic profile of *R*-warfarin and that prothrombin times were not significantly altered by concomitant meloxicam treatment. However, for *S*-warfarin, slightly higher (+11%) plasma concentrations and steady state AUC were observed with concomitant meloxicam use. Because meloxicam and *S*-warfarin are metabolized by the same CYP isoenzyme, it is recommended that patients receiving both medications be closely monitored (Mobic US PI, 2012; Davies NM and Skjodt NM, 1999).

A review of the published literature did not produce any information documenting an effect of meloxicam on QT interval or any potential drug-drug interactions with drugs known to result in QT prolongation (5.4 Literature References).

2.7.2.4.1.9 Drug-Disease Interactions

2.7.2.4.1.9.1 CARDIOVASCULAR DISEASE

Class labeling for NSAIDs includes a warning that CV effects, including hypertension, edema, congestive heart failure, and CV thrombotic events, have been observed in patients receiving these agents. Clinical trials of several COX-2 selective and nonselective NSAIDs for up to 3 years duration have demonstrated an increased risk of serious CV thrombotic events, myocardial infarction, and stroke, which could be fatal ([Mobic US PI, 2012](#)). The increased risk for these events is present following initiation of treatment with these agents based on observational studies ([Odom D et al, 2014](#)) and has been demonstrated for COX-2 selective and nonselective NSAIDs ([Mobic US PI, 2012](#)). Patients with known CV disease or risk factors for CV disease or who underwent coronary artery bypass surgery may be at greater risk for the development of serious CV events ([Mobic US PI, 2012](#)). Changes in the meloxicam pharmacokinetic profile due to CV disease have not been documented.

The proposed Vivlodex Capsules Prescribing Information ([1.14.1.3 Draft Labeling Text](#)) reflects the expectation for class labeling as for other NSAIDs.

2.7.2.4.1.9.2 ULCER DISEASE AND GASTROINTESTINAL BLEEDING

Class labeling for NSAIDs includes a warning that NSAIDs, including meloxicam, can cause serious GI AEs including inflammation, bleeding, ulceration, and perforation of the esophagus, stomach, small intestine, or large intestine, which can be fatal ([Mobic US PI, 2012](#)). NSAIDs should be prescribed with extreme caution in those with prior history of ulcer disease or GI bleeding (FDA Proposed NSAID Package Insert Labeling Template 1; [Mobic US PI, 2012](#)). Patients with a prior history of peptic ulcer disease and/or GI bleeding who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to patients with neither of these risk factors. Other factors that increase the risk for GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore, special care should be taken in treating this population. Changes in the meloxicam pharmacokinetic profile due to GI disease have not been documented.

As previously stated, meloxicam metabolism is P450-mediated. The human cytochrome P450 (CYP) isoform, CYP2C9 (and to a lesser extent CYP3A4), converts meloxicam to its 5'-hydroxymethyl metabolite. An association of variant CYP2C9 alleles and the risk of acute GI bleeding have shown a gene-dose effect, which is higher in patients receiving drugs that are metabolized primarily by CYP2C9 ([Martinez C, et al, 2004](#)). CYP2C9-genotyping has been proposed to identify individuals who are at an increased risk of acute GI bleeding ([Martinez C, et al, 2004](#)). A 2005 publication surveyed a number of COX inhibitors and performed kinetic calculations to determine whether the CYP2C9 genotype would influence drug clearance. Based on the calculations, the CYP2C9 genotype is expected to influence the clearance of meloxicam ([Rodrigues AD, 2005](#)); however, currently, there are no reports that describe the effects of the CYP2C9 genotype on meloxicam pharmacokinetic parameters.

The proposed Vivlodex Capsules Prescribing Information (1.14.1.3 Draft Labeling Text) reflects the expectation for class labeling as for other NSAIDs.

2.7.2.4.1.9.3 RENAL INSUFFICIENCY

Class labeling for NSAIDs includes a warning that renal effects have been reported in patients treated with selective and non-selective COX-2 inhibitors (FDA Proposed NSAID Package Insert Labeling Template 1). Renal toxicity is noted in patients in whom renal prostaglandins play a compensatory role in the maintenance of renal perfusion. In these patients, administration of NSAIDs may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation (Mobic US PI, 2012). These effects on renal function are considered reversible following NSAID discontinuation. Patients at greatest risk of experiencing renal effects are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, angiotensin II receptor antagonists, and ACE inhibitors, and the elderly.

The Mobic PI indicates that no dosage adjustments in patients with mild and moderate renal impairment are required. The published literature supports this claim. A 1997 trial evaluating meloxicam pharmacokinetic parameters in patients with mild renal impairment found that no significant differences in meloxicam pharmacokinetics between individuals with normal (creatinine clearance [CL_{CR}] >60 mL/min [>3.6 L/h]) and mildly impaired (CL_{CR} 41 to 60 mL/min [2.5 to 3.6 L/h]) renal function (Boulton-Jones JM, et al, 1997). A 1996 publication noted similar results in a 28-day trial of meloxicam 15 mg/day in patients with mild azotemia (Bevis PJ, et al, 1996), while the 1997 trial noted lower total meloxicam plasma concentrations and higher plasma clearances in patients with moderate azotemia compared with healthy subjects (Boulton-Jones JM, et al, 1997, Davies NM and Skjodt NM, 1999).

Following a single oral dose of meloxicam 15 mg capsules, meloxicam pharmacokinetics were compared between 12 patients with end-stage renal disease (ESRD) and age-matched controls. Patients with ESRD demonstrated lower total meloxicam plasma concentrations compared with healthy subjects. Additionally, these patients had increased free fractions of meloxicam (0.9% compared with 0.3% in controls), but greater relative total meloxicam clearance (+211% compared with controls); therefore, the greater free fraction of meloxicam was compensated for by the increased clearance so that no accumulation of meloxicam occurred (Türck D, et al, 1996). Due to the higher C_{max} values, it is recommended that a lower meloxicam dosage (7.5 mg) be administered to patients with ESRD (Türck D, et al, 1996).

The proposed Vivlodex Capsules Prescribing Information (1.14.1.3 Draft Labeling Text) reflects the expectation for class labeling as for other NSAIDs.

2.7.2.4.1.9.4 HEPATIC INSUFFICIENCY

Class labeling for NSAIDs includes a warning regarding hepatic effects (FDA Proposed NSAID Package Insert Labeling Template 1). Borderline elevations of 1 or more liver function tests (LFTs) may occur in up to 15% of patients taking NSAIDs. These abnormalities in LFTs may progress, may remain unchanged, or may be transient with

continuing therapy. Notable elevations of alanine aminotransferase or aspartate aminotransferase approximately 3 or more times the upper limit of normal have been reported in approximately 1% of patients in clinical trials with NSAIDs (Mobic US PI, 2012).

Following a single 15 mg dose of meloxicam there was no marked difference in plasma concentrations in patients with mild (Child-Pugh Class I) or moderate (Child-Pugh Class II) hepatic impairment compared to healthy volunteers (Mobic US PI, 2012). Additionally, protein binding of meloxicam was not affected by hepatic impairment. No dosage adjustment is necessary in patients with mild to moderate hepatic impairment. There have not been studies that include patients with severe hepatic impairment (Child-Pugh Class III) (Mobic US PI, 2012).

Meloxicam pharmacokinetics following a single oral dose of 15 mg were investigated in 12 patients with clinically stable liver cirrhosis. Minor differences in pharmacokinetic parameters were observed in patients with liver cirrhosis compared with healthy subjects. Meloxicam C_{max} and t_{max} were 0.84 mg/L and 10.3 hours, respectively, in patients with liver cirrhosis; healthy volunteers demonstrated meloxicam C_{max} and t_{max} of 0.91 mg/L and 7.0 hours (Busch U, et al, 1996). The meloxicam $t_{1/2}$ was approximately 5 hours faster than healthy subjects, and the AUC was approximately 25% lower in cirrhotic patients. No relevant differences in plasma protein binding of meloxicam were seen. No considerable changes in the meloxicam pharmacokinetic profile were demonstrated in hepatically impaired patients, and therefore, this trial did not deem dosage adjustments necessary (Busch U, et al, 1996).

It is anticipated that Vivlodex Capsules will have similar class labeling as other meloxicam products.

2.7.2.4.1.9.5 HYPERTENSION

Class labeling for NSAIDs includes a warning regarding hypertension (FDA Proposed NSAID Package Insert Labeling Template 1). NSAIDs, including meloxicam, can lead to new onset of hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events (Mobic US PI, 2012).

Patients taking ACE inhibitors, thiazides, or loop diuretics may have impaired antihypertensive response to these therapies when taking NSAIDs. NSAIDs, including meloxicam, should be used with caution in patients with hypertension. Blood pressure should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy (Mobic US PI, 2012).

2.7.2.4.1.9.6 PREEXISTING ASTHMA

Class labeling for NSAIDs includes a warning that patients with asthma may have aspirin-sensitive asthma (FDA Proposed NSAID Package Insert Labeling Template 1). The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm, which could be fatal. Since cross reactivity between aspirin and other NSAIDs has been reported in aspirin-sensitive asthmatic patients, meloxicam should not be

administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma ([Mobic US PI, 2012](#)). Changes in the meloxicam pharmacokinetic profile due to asthma have not been documented.

2.7.2.4.1.10 Pregnancy and Lactation

Meloxicam is known to cross the placenta and its use is not recommended during pregnancy, especially ≥ 30 weeks of gestation. Meloxicam has been shown in animal models to have teratogenic and nonteratogenic effects on fetuses. When administered to pregnant rabbits at an oral dose of 60 mg/kg/day, meloxicam caused an increased incidence of septal heart defects in rabbit embryos. The no effect level was 20 mg/kg/day (26-fold greater than the maximum recommended human dose [MRHD] based on body surface area [BSA] conversion) ([Mobic US PI, 2012](#)). Embryo lethality in rats and rabbits occurred at oral doses of 1 mg/kg/day and 5 mg/kg/day, respectively (0.65- and 6.5-fold greater, respectively, than the MRHD based on BSA conversion) when treated throughout organogenesis. Meloxicam was not teratogenic in rats up to an oral dose of 4 mg/kg/day (approximately 2.6-fold the human dose, as noted above) throughout organogenesis. There are no adequate and well-controlled studies in pregnant women ([Mobic US PI, 2012](#)).

Meloxicam increased the incidence of dystocia, delayed parturition, and decreased offspring survival at oral doses ≥ 0.125 mg/kg/day (at least 12.5-fold lower than the MRHD based on BSA conversion) when rats were treated during the late gestation and lactation period. A review of the published literature did not produce any information on the effect of meloxicam on the closure of the ductus arteriosus in humans ([5.4 Literature References](#)). It is recommended that use of meloxicam during the third trimester of pregnancy be avoided.

It is not known if meloxicam is excreted in human breast milk; however, meloxicam was excreted in the milk of lactating rats at concentrations higher than those in plasma ([Mobic US PI, 2012](#)). Safety concerns related to pregnancy and fetal outcome are discussed in more detail in [2.7.4 Summary of Clinical Safety, Section 2.7.4.6.5](#).

2.7.2.4.1.11 Population Pharmacokinetics in Patients and Healthy Subjects

The literature search provided one previous population pharmacokinetic study with meloxicam in humans ([Meineke I and Türck D, 2003](#)). A nonlinear mixed effect modeling analysis was conducted on plasma samples derived from 586 patients with RA participating in 3 clinical trials to evaluate the effects of age, weight, gender, and concomitant medications on meloxicam pharmacokinetics. The data were adequately described by a 1-compartmental model. In the covariate analysis, age and gender both significantly ($P < 0.005$) affected meloxicam clearance; however, the age effect was relatively small, requiring only a $< 10\%$ dose adjustment, and the gender effect was attributed to differences in body weight. While no clinically relevant drug-drug interactions were found, it was reported that sulphasalazine and glucocorticoids significantly ($P < 0.005$) affected meloxicam clearance (+19% and -12%, respectively) ([Meineke I and Türck D, 2003](#)).

A population pharmacokinetic study ([Meloxicam Population PK Analysis Report](#)) was performed with Vivlodex Capsules by Iroko. The goal of the study was to use data from the Phase 1 PK trials [QP09C03](#) and [MEL1-11-01](#) to develop and validate a Population

Pharmacokinetic Model to determine whether Vivlodex Capsules 5 mg and 10 mg would achieve a pharmacokinetic profile that would result in a similar C_{max} and a >20% reduction in AUC compared with Mobic 7.5 mg and 15 mg tablets, respectively. Results from this analysis confirmed that, under fasted conditions, Vivlodex Capsules 5 mg and 10 mg would likely meet the target product pharmacokinetic profile mentioned above ([Meloxicam Population PK Analysis Report](#)). Vivlodex Capsules 5 mg and 10 mg safety and efficacy have recently been evaluated in 2 Phase 3 trials, [MEL3-12-02](#) and [MEL3-12-03](#) ([2.7.3 Summary of Clinical Efficacy](#), [2.7.4 Summary of Clinical Safety](#)).

2.7.2.4.1.12 Pharmacodynamic Dose-Range and Dose-Response Clinical Trials

It has been noted that establishing relationships between plasma concentrations of NSAIDs, dosage regimens, and clinical effects is difficult ([Davies NM and Skjodt NM, 1999](#)). A randomized, double-blind, double-dummy trial included 113 subjects with acute sciatica who were treated with a single dose of 15 mg meloxicam administered IM or orally to evaluate pain relief. Both treatments demonstrated significant pain relief compared with placebo, but IM meloxicam relieved pain in acute sciatica significantly more rapidly than did oral meloxicam ([Auvinet B, et al, 1995](#)). The authors proposed that one explanation for the increased efficacy with IM meloxicam was due to the faster t_{max} of IM administration (1 hour) compared with oral meloxicam capsules (cited as 8 to 9 hours from [Narjes H, et al, 1996](#)). The considerable variation reported in the t_{max} of meloxicam depending on route of administration and the concomitant use of other drugs that complicates clinical use has been noted ([Davies NM and Skjodt NM, 1999](#)). It has been suggested that further studies are required to address the effects of free meloxicam on inflammatory mediators and clinical efficacy. As seen with other NSAIDs, meloxicam is likely to demonstrate tissue, plasma, and urine concentration-effect relationships ([Davies NM and Anderson KE, 1997](#)).

The relationship between meloxicam dose and analgesic effects of Vivlodex Capsules is described in [2.7.3 Summary of Clinical Efficacy](#).

2.7.2.5 Special Studies

Not applicable.

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

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

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	NDA-207233	Brand Name	Vivlodex
OCP Division (I, II, III, IV, V)	II	Generic Name	Meloxicam
Medical Division	DAAAP	Drug Class	NSAID
OCP Reviewer	Suresh B Naraharisetti	Indication(s)	Chronic pain
OCP Team Leader	Yun Xu	Dosage Form	Immediate-release Capsule
Pharmacometrics Reviewer		Dosing Regimen	5 or 10 mg QD
Date of Submission	12/23/2014	Route of Administration	Oral
Estimated Due Date of OCP Review		Sponsor	Iroko Pharma
Medical Division Due Date		Priority Classification	
PDUFA Due Date	10/ 23/ 2015		

Clin. Pharm. and Biopharm. Information

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

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hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	1		Mobic (NDA020938) as reference
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	X	1		
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				Yes
Literature References				
Total Number of Studies		4		

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

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					

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

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

Yes

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

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

BACKGROUND

Iroko Pharmaceuticals submitted a 505 (b) (2) NDA (207233) for Vivlodex capsules for the management of osteoarthritis pain in adults. As a 505(b) (2) NDA Sponsor is relying on the Agency's findings on the safety and efficacy of Mobic, NDA 020938 (7.5 and 15 mg tablets). For establishing the clinical bridge, Iroko has conducted a relative bioavailability (BA) against Mobic 15 mg tablets.

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

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Clinical Pharmacology Studies:

- **Phase 1 MEL1-12-04:** Relative BA, food effect and dose proportionality study (pivotal study with commercial formulation)
 - Design: A randomized, 4-period, 4-treatment, 4-sequence, single-dose, crossover, pharmacokinetic trial of meloxicam test capsules 5 mg and 10 mg and mobic® 15 mg in healthy subjects (n=25).
 - This study was conducted with commercial scale formulation. The study is pivotal study assessing relative bioavailability, dose proportionality and food effect of Vivlodex capsules.

Clinical Studies:

- **Phase 3 MEL3-12-02 - Pivotal trial (with commercial formulation):**
 - Design: A Phase 3, multicenter, randomized, double-blind, double-dummy, placebo-controlled, fixed-dose, parallel-group, efficacy, and safety study of meloxicam test capsules in patients with pain due to osteoarthritis of the knee or hip (n= 402)
 - This study was conducted with a commercial scale formulation
- **Phase 3 MEL3-12-03 (with commercial formulation):**
 - Design: A multicenter, open-label, safety study of meloxicam test capsules in subjects with osteoarthritis of the knee or hip (n=390)
 - This study was conducted with a commercial scale formulation

Suresh Babu Naraharisetti	January 22, 2015
Reviewing Clinical Pharmacologist	Date
Xu Yun	January 22, 2015
Team Leader/Supervisor	Date

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

/s/

SURESH B NARAHARISSETTI
01/22/2015

YUN XU
01/26/2015