

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**207233Orig1s000**

**PHARMACOLOGY REVIEW(S)**

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

**PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION**

NDA application number:	207233
Supporting document/s:	SD 1, 4 and 5
Applicant's letter date:	December 23, 2014
CDER stamp date:	December 23, 2014
Product:	Vivlodex™ (meloxicam) oral capsules
Indication:	Management of osteoarthritis (OA) pain
Applicant:	Iroko Pharmaceuticals, LLC
Review Division:	Division of Anesthesia, Analgesia, and Addiction Products
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# 1 Executive Summary

## 1.1 Introduction

Vivlodex™ (meloxicam) is a non-steroidal anti-inflammatory drug (NSAID) for the (b) (4) of osteoarthritis (OA) pain. Iroko Pharmaceuticals, LLC has submitted NDA 207233 for marketing approval of Vivlodex as a 505(b)(2) application with reference made to NDA 20938 (Mobic® - Boehringer Ingelheim, approved 4/13/2000) to rely on the Agency's previous findings of safety and efficacy for the approved listed drug and for support of current product labeling of meloxicam.

Vivlodex capsules are a new meloxicam drug product using SoluMatrix particle sizing technology to reduce the drug substance particle size and enhance the rates of dissolution and absorption of meloxicam in the gastrointestinal (GI) tract. The goal of this technology is to permit a lower therapeutic dose while achieving similar plasma exposures to currently approved oral meloxicam doses.

Vivlodex will be available as 5 mg and 10 mg oral capsules, and will be administered as one capsule by mouth once daily with a usual dose of 5 or 10 mg per day. In comparison, Mobic is available as 7.5 mg and 15 mg oral tablets, and is administered once daily. Note that a comparative bioavailability study in healthy human subjects showed that  $C_{max}$  values were similar after single doses of Vivlodex at 5 and 10 mg compared to Mobic at 7.5 and 15 mg, respectively, but AUC values were approximately 33% less with Vivlodex at 5 and 10 mg compared to Mobic at 7.5 and 15 mg, respectively.

There are no novel excipients in the Vivlodex drug product and no impurities or degradation products in the meloxicam drug substance and Vivlodex drug product that exceed ICH regulatory thresholds, with the exception of a potential genotoxic impurity (b) (4) (referred to as (b) (4) which exceeds the acceptable daily intake of NMT 1.5 mcg/day in the drug substance in accordance with ICH M7 guideline recommendations. However, the Applicant is controlling levels of this impurity in the drug product by setting a specification of NMT (b) (4)%, or (b) (4) mcg/day based on a Vivlodex dose of 10 mg/day, which is considered acceptable.

Therefore additional nonclinical studies are not required to support the safety of this drug product formulation.

## 1.2 Brief Discussion of Nonclinical Findings

The Vivlodex Capsules nonclinical program was based on the safety profile of Mobic and on the published pharmacology, PK and toxicology literature. Thus no new nonclinical studies were conducted by the Applicant except for a computational genotoxicity assessment.

An in silico computational genotoxicity evaluation of three known meloxicam-related impurities was conducted in order to assess their genotoxic potential. This assessment employed the CASE Ultra MC4PC modules, and the output of the

Informatics and Computational Safety Analysis Staff (ICSAS) method expert call for the 3 impurities. The Applicant concluded that there was no evidence of genetic toxicity to humans for two impurities, (b) (4) based on the results of the in silico computational analysis. The third meloxicam-related impurity, (b) (4) demonstrated evidence of potential genotoxicity due to confirmation of a structure-activity alert. Rather than conducting additional nonclinical evaluations to qualify the safety of this impurity, the Applicant has tightened the specification for (b) (4) to be in accordance with the acceptable daily intake of NMT 1.5 mcg/day per the ICH M7 guidance for industry.

To confirm the Applicant's conclusion for evidence of potential genotoxicity, these three impurities were evaluated by FDA/CDER/OTS/OCP/DARS for bacterial mutagenicity using (quantitative) structure-activity relationship [(Q)SAR] models. Based on the result, (b) (4) was predicted to be positive for bacterial mutagenicity and the other two were predicted to be negative for bacterial mutagenicity (See Attachment 1).

### **1.3 Recommendations**

#### **1.3.1 Approvability:**

From the nonclinical pharmacology toxicology perspective, this NDA may be approved.

#### **1.3.2 Additional Non Clinical Recommendations:**

None

#### **1.3.3 Labeling:**

The table below shows the Applicant's proposed label language included with the original NDA submission, this reviewer's recommended changes to the proposed language, and the rationale for this reviewer's recommended changes. My recommended changes include revisions per the Pregnancy and Lactation Labeling Rule and incorporate NSAID label template language that has recently been required by the Agency for all approved NSAID drug products. Note, that the final label may differ based on further internal discussion. Therefore, refer to the Action Letter for final labeling for this drug product.

Applicant's Proposed Labeling	Recommended changes to proposed labeling	Rationale for recommended changes
<p><b>8.1 Pregnancy</b></p> <p>(b) (4)</p>	<p><b>8.1 Pregnancy</b></p> <p><b>Risk Summary</b></p> <p><i>Use of NSAIDs, including VIVLODEX, during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including VIVLODEX, in pregnant women starting at 30 weeks of gestation (third trimester).</i></p> <p><i>There are no adequate and well-controlled studies of VIVLODEX in pregnant women. Data from observational studies regarding potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive. In the general U.S. population, all clinically recognized pregnancies, regardless of drug exposure, have a background rate of 2-4% for major malformations, and 15-20% for pregnancy loss. In animal reproduction studies, embryofetal death was observed in rats and rabbits treated during the period of organogenesis with meloxicam at oral doses equivalent 1- and 10-times, respectively, the maximum recommended daily dose (MRDD) of VIVLODEX. Additionally, increased incidence of septal heart defects were observed in rabbits treated throughout embryogenesis with meloxicam at an oral dose equivalent to 116-times the MRDD. In pre- and post-natal reproduction studies, increased incidence of dystocia, delayed parturition, and decreased offspring survival were observed in rats treated with meloxicam at an oral dose equivalent to 0.12-times the MRDD of VIVLODEX. No teratogenic effects were observed in rats treated with</i></p>	<p>This section was revised per the Pregnancy and Lactation Labeling Rule (PLLR) published on 12/04/2014.</p> <p>(b) (4)</p> <p>nd a narrative summary of the risks was added per PLLR.</p> <p>In addition, required language from a recently released NSAID label template has been added and is indicated in italics.</p> <p>Exposure margins were modified based on the Applicant's proposed maximum recommended daily dose of 10 mg of VIVLODEX. Note that a comparative bioavailability study in healthy human subjects showed that AUC values were approximately 33% less with Vivlodex at 5 and 10 mg compared to Mobic at 7.5 and 15 mg, respectively, which correlates with the 33% lower meloxicam dosage strength.</p>

	(b) (4)	<p>meloxicam during organogenesis at an oral dose equivalent to 3.9- times the MRDD [See Data]. Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as [meloxicam], resulted in increased pre- and post-implantation loss.</p> <p><i>Clinical Considerations</i>  <i>Labor or Delivery</i>  There are no studies on the effects of VIVLODEX during labor or delivery. In animal studies, NSAIDS, including meloxicam, inhibit prostaglandin synthesis, cause delayed parturition, and increase the incidence of stillbirth.</p> <p><i>Data</i>  <i>Human Data</i>  (See clinical reviews for recommendations)</p> <p><i>Animal data</i>  Meloxicam was not teratogenic when administered to pregnant rats during fetal organogenesis at oral doses up to 4 mg/kg/day (3.9-times the maximum recommended daily dose (MRDD) of 10 mg of VIVLODEX based on body surface area [BSA] comparison). Administration of meloxicam to pregnant rabbits throughout embryogenesis produced an increased incidence of septal defects of the heart at an oral dose of 60 mg/kg/day (116-fold times the MRDD based on BSA comparison). The no effect level was 20 mg/kg/day (39-times the MRDD based on BSA comparison).</p> <p>In rats and rabbits, embryoletality occurred at oral meloxicam doses of 1 mg/kg/day</p>
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	<p>and 5 mg/kg/day, respectively (1- and 10-times the MRDD based on BSA comparison) when administered throughout organogenesis.</p> <p>Oral administration of meloxicam to pregnant rats during late gestation through lactation increased the incidence of dystocia, delayed parturition, and decreased offspring survival at meloxicam doses of 0.125 mg/kg/day or greater (0.12-times the MRDD based on BSA comparison).</p>	
<p><b>8.2</b> (b) (4)                  (b) (4)</p>	<p><b>8.2 Lactation</b>  <i>Risk Summary</i>                  It is not known whether this drug is excreted in human milk. <i>The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VIVLODEX and any potential adverse effects on the breastfed infant from the VIVLODEX or from the underlying maternal condition.</i></p> <p>In animal studies, meloxicam was excreted in the milk of lactating rats at concentrations higher than those in plasma.</p>	<p>Per PLLR, (b) (4)                  (b) (4)</p> <p>Language in italics is from NSAID label template.</p> <p>Language regarding nonclinical data is from Mobic label.</p>
<p><b>8.3</b> (b) (4)                  (b) (4)</p>	<p><b>8.3 Females and Males of Reproductive Potential</b>  <i>Infertility</i>  <i>Females</i>  <i>Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including VIVLODEX, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin-mediated follicular rupture required for ovulation. Small studies in women treated with NSAIDs</i></p>	<p>Per PLLR, Section 8.3 is for information on females and males of reproductive potential, including data indicating risk for infertility. The language included here is from the NSAID label template (in italics).</p>

	<p><i>have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including VIVLODEX, in women who have difficulties conceiving or who are undergoing investigation of infertility.</i></p>	
	<p><b>12.1 Mechanism of Action</b>  <i>VIVLODEX has analgesic, anti-inflammatory, and antipyretic properties.</i></p> <p><i>The mechanism of action of VIVLODEX, like that of other NSAIDs, is not completely understood but involves inhibition of cyclooxygenase (COX-1 and COX-2).</i></p> <p><i>Meloxicam is a potent inhibitor of prostaglandin synthesis in vitro. meloxicam concentrations reached during therapy have produced in vivo effects. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of inflammation. Since meloxicam is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.</i></p>	<p>Language in italics is from the NSAID label template.</p>
<p><b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b>  <span style="background-color: #cccccc; display: inline-block; width: 200px; height: 100px; vertical-align: middle;"></span> (b) (4)</p>	<p><b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b></p> <p><u>Carcinogenesis</u>          There was no increase in tumor incidence in long-term carcinogenicity studies in rats (104 weeks) and mice (99 weeks) administered meloxicam at oral doses up to 0.8 mg/kg/day in rats and up to 8.0 mg/kg/day in mice (up to 0.8- and 3.9-times, respectively, the maximum recommended daily dose (MRDD) of 10 mg of VIVLODEX based on body surface area comparison).</p>	<p>The Applicant stated here that <span style="background-color: #cccccc; display: inline-block; width: 100px; height: 20px; vertical-align: middle;"></span> (b) (4)  <span style="background-color: #cccccc; display: inline-block; width: 100px; height: 20px; vertical-align: middle;"></span> (b) (4)</p> <p><span style="background-color: #cccccc; display: inline-block; width: 100px; height: 20px; vertical-align: middle;"></span> (b) (4) However Section 12.3 states that VIVLODEX 10 mg capsules do not result in an equivalent systemic exposure compared to 15 mg meloxicam tablets. Rather, the 33% lower dose of meloxicam in VIVLODEX resulted in a 33% lower overall systemic exposure. Therefore, the Applicant's statement is omitted and</p>

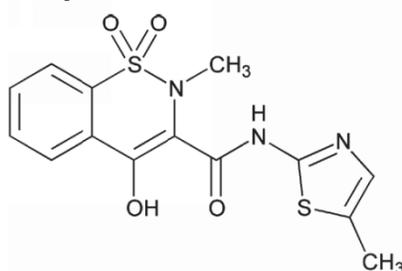
(b) (4)	<p><u>Mutagenesis</u> Meloxicam was not mutagenic in an Ames assay, or clastogenic in a chromosome aberration assay with human lymphocytes and an in vivo micronucleus test in mouse bone marrow.</p> <p><u>Impairment of Fertility</u> There was no impairment of male or female fertility in rats at oral doses up to 9 mg/kg/day in males and 5 mg/kg/day in females (up to 8.7 and 4.8-times, respectively, the MRDD based on body surface area comparison).</p>	safety margins have been modified to reflect the lower VIVLODEX dose.
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## 2 Drug Information

### 2.1 Drug

<b>CAS Registry Number</b>	71125-38-7
<b>Generic Name</b>	Meloxicam
<b>Code Name</b>	Vivlodex™
<b>Chemical Name</b>	4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide
<b>Molecular Formula</b>	C <sub>14</sub> H <sub>13</sub> N <sub>3</sub> O <sub>4</sub> S <sub>2</sub>
<b>Molecular Weight</b>	351.4 g/mole

## Structure or Biochemical Description



**Pharmacologic Class** NSAIDs (nonsteroidal anti-inflammatory drugs)

## 2.2 Relevant INDs, NDAs, BLAs and DMFs

The Applicant provided a letter of authorization to DMF (b) (4). Meloxicam drug substance is manufactured and supplied by Cadila Healthcare Limited.

Application	Status/date	Sponsor	Subject	Indication/Comment
IND 114045	Active (12/22/2011)	Iroko	Meloxicam solumatrix capsules	Osteoarthritis pain
NDA 020938	Approved 04/13/2000	Boehringer Ingelheim	Mobic® Tablets 7.5 & 15 mg	Long term use in the relief of signs & symptoms of OA & RA
DMF (b) (4)	Active (8/9/2004)	(b) (4)	Meloxicam	LOA provided. DMF adequate as per CMC review team
DMF (b) (4)	Active (11/8/1978)	(b) (4)	(b) (4)	LOA provided. DMF adequate as per CMC review team

## 2.3 Drug Formulation

Vivlodex™ is available in 2 capsule strengths, 5 mg and 10 mg. Both strengths are manufactured from a (b) (4) encapsulated in hard gelatin capsule shells.

**Composition of Vivlodex Capsules 5 mg**

Component	Amount per capsule (mg/capsule weight)	Function	Quality Standard
Meloxicam	5.00	Active pharmaceutical ingredient	USP
Lactose monohydrate	(b) (4)	(b) (4)	NF
Sodium lauryl sulfate	(b) (4)	(b) (4)	NF
Microcrystalline cellulose	(b) (4)	(b) (4)	NF
Croscarmellose sodium	(b) (4)	(b) (4)	NF
Sodium stearyl fumarate	(b) (4)	(b) (4)	NF
Total capsule fill weight	125.0	--	--
Size 2 capsule with light pink body with "IP-205" imprinted in white ink and a dark blue cap with "5 mg" imprinted in white ink containing a yellow to pale yellow (b) (4)	1 capsule	Capsule shell	(b) (4)

**Composition of Vivlodex Capsules 10 mg**

Component	Amount per capsule (mg/capsule weight)	Function	Quality Standard
Meloxicam	10.00	Active pharmaceutical ingredient	USP
Lactose monohydrate	(b) (4)	(b) (4)	NF
Sodium lauryl sulfate	(b) (4)	(b) (4)	NF
Microcrystalline cellulose	(b) (4)	(b) (4)	NF
Croscarmellose sodium	(b) (4)	(b) (4)	NF
Sodium stearyl fumarate	(b) (4)	(b) (4)	NF
Total capsule fill weight	250.0	--	--
Size 1 capsule with pink body with "IP-206" imprinted in white ink and a dark blue cap with "10 mg" imprinted in white ink containing a yellow to pale yellow (b) (4)	1 capsule	Capsule shell	(b) (4)

The Applicant has an LOA for DMF (b) (4) to use information on the 2 piece hard gelatin empty capsule shells manufactured by (b) (4)

**Ingredients for the Size 2 and Size 1 Dark Blue Cap With  
White Ink Used for Vivlodex Capsules 5 mg and 10 mg**

Ingredient	Acceptance Criteria
FD&C blue #2	FD&C
Titanium dioxide	NF
Gelatin	NF
Ink – White (b) (4)	Edible ink FDA Inactive ingredients list <sup>a</sup>

<sup>a</sup> Application for oral capsule

**Ingredients for the Size 2 Light Pink Body With White Ink  
Used for Vivlodex Capsules 5 mg**

Ingredient	Acceptance Criteria
Carmine	FD&C
Titanium dioxide	NF
Gelatin	NF
Ink – White (b) (4)	Edible ink FDA Inactive ingredients list <sup>a</sup>

<sup>a</sup> Application for oral capsule

**Ingredients for Size 1 Pink Body With White Ink Used for  
Vivlodex Capsules 10 mg**

Ingredient	Acceptance Criteria
FD&C red #40	FD&C
FD&C yellow #6	FD&C
Titanium dioxide	NF
Gelatin	NF
Ink – White (b) (4)	Edible ink FDA Inactive ingredients list <sup>a</sup>

<sup>b</sup> Application for oral capsule

## 2.4 Comments on Novel Excipients

All of the excipients are within levels found in oral drug products approved for chronic use based on maximum potency levels listed in the FDA inactive ingredient database (IID) and the dosing information provided by the approved drug labels. The table below shows the excipient composition of Vivlodex 10 mg capsules and compares the amount per capsule with relevant maximum potency information from the IID.

### ***Adequacy of excipients in 10 mg meloxicam capsules:***

Component	Amount per capsule	IID Maximum potency (Oral route)	Comment on adequacy for chronic indication
Lactose monohydrate	(b) (4)	(b) (4)	Has been used for chronic indication where the maximum daily dose is 180 mg lactose

			monohydrate
Sodium lauryl sulfate	(b) (4)		Has been used for chronic indication where the maximum daily dose is 10 mg Sodium lauryl sulfate
Microcrystalline cellulose			Has been used for chronic indication where the maximum daily dose is up to 328.36 mg Microcrystalline cellulose
Croscarmellose sodium			Has been used for chronic indication where the maximum daily dose is up to 36 mg Croscarmellose sodium
Sodium stearyl fumarate			Has been used for chronic indication where the maximum daily dose is 8.1 mg sodium stearyl fumarate

All of the inactive ingredients in the capsule shells are within maximum potency levels listed in the IID levels for oral products approved for chronic indications.

***Adequacy of gelatin empty capsule shells:***

component	Amount in capsule mg/capsule	IID Maximum potency (Oral route)	Chronic use
FD&C blue # 2	(b) (4)		Has been used for chronic indication where the maximum daily dose is 1.13 mg
FD&C red # 40			Has been used for chronic indication where the maximum daily dose is 1.17 mg
FD&C yellow # 6			Has been used for chronic indication where the maximum daily dose is 0.03 mg
Titanium dioxide			Has been used for chronic indication where the maximum daily dose is 5.75 mg
Gelatin			<b>GRAS</b> and has been used for chronic indication where the maximum daily dose is 60 mg
Carmine			Has been used for chronic indication where the maximum daily dose is 0.15 mg
Ink-white- (b) (4)	(b) (4)	Potency not given	This printing ink has been used for chronic indication. Potency generally listed as quantity sufficient Use is consistent with other approved products.

**2.5 Comments on Impurities/Degradants of Concern**

There are three potential impurities that originate from the meloxicam drug substance. See table below provided by the Applicant that lists the impurity name, origin, specification limit, and maximum calculated amount in Vivlodex Capsules.

Chemical Name	Other Names	Origin	Meloxicam Drug Substance Specification	Maximum theoretical amount in Vivlodex Capsules
(b) (4)	Meloxicam Known Related (b) (4)	Stability indicating and process related	NMT (b) (4) %	Below detectable limits (b) (4)
(b) (4)	Meloxicam Known Related (b) (4)	Process related	NMT (b) (4) %	Below detectable limits (b) (4)
(b) (4)	(b) (4)	Process related	NMT (b) (4) %	Below detectable limits (b) (4)

The Applicant provided a letter of authorization to DMF (b) (4). The table below lists the impurity specifications for the meloxicam drug substance used in the manufacture of the commercial drug product. The (b) (4) specification of NMT (b) (4) % in the drug substance raises a concern since it is a potential genotoxic impurity and this impurity should be kept within the acceptable intake of NMT 1.5 mcg/day. However, the Applicant is controlling the level of this impurity in the drug product with an acceptable specification of NMT (b) (4) %, (b) (4) potential total daily intake to NMT 1.5 mcg/day.

**Meloxicam Drug Substance Specifications:**

Test	Method	Acceptance Criteria
Related Compounds by HPLC:		--
Meloxicam related (b) (4)	(b) (4)	NMT (b) (4) %
(b) (4)		NMT %
Individual unknown impurity		NMT %
Total impurities	(b) (4)	NMT %

Table below lists the release and shelf-life specification for Vivlodex capsules 5 mg and 10 mg.

**Meloxicam Drug Product Specification:**

Test	Method	Acceptance Criteria
Meloxicam related substances	HPLC assay and related substances	Meloxicam Related (b) (4) NMT (b) (4) %
Individual unknown impurities		NMT (b) (4) %
Total impurities		NMT (b) (4) %

The specifications for these three impurities are below the qualification thresholds described in ICH Q3A(R2) for drug substance (b) (4) % and ICH Q3B(R2) for drug product (b) (4) % for 5 mg and 10 mg doses).

Note that the Applicant conducted an in silico computational assessment of genotoxicity for these three impurities and based on the results (see Genetic toxicology section for more detail), it was concluded that only (b) (4) Meloxicam Related (b) (4) showed a structure activity relationship that indicated potential genotoxicity to humans. Therefore, the (b) (4) specification of NMT (b) (4) % in drug product is acceptable since the impurity level is below the toxicologic threshold of concern (TTC) limit of 1.5 mcg/day in accordance with the ICH M7 guidance.

**2.6 Proposed Clinical Population and Dosing Regimen**

Vivlodex (Meloxicam SoluMatrix Oral Capsule), a submicron particle formulation, is intended for the management of OA pain in adults. The dosage regimen is 5 mg or 10 mg once daily.

**2.7 Regulatory Background**

- The Applicant submits a 505(b)(2) application referencing meloxicam, as an oral tablet (NDA 20938 Mobic® - Boehringer Ingelheim, approved 4/13/2000).
- Related IND 114045 is active since 01/20/2012.
- From EOP2 meeting on November 13, 2012:

*Assuming that the reformulated product does not produce clinical exposure to meloxicam which exceeds that of the referenced product, we agree that additional nonclinical studies are not required to support the safety of meloxicam for Phase 3 studies or the NDA submission. However, any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety for the NDA submission.*

- From pre-NDA meeting on July 16, 2014:

*Based on the information provided in the meeting package, we agree that no additional nonclinical studies are required.*

*However, we note that due to increased bioavailability with your drug product, your total daily dose is lower than the referenced drug product yet provides comparable exposure levels. Most of the nonclinical data in the referenced drug product labeling includes exposure margins that are based on body surface extrapolations. Exposure margins are necessary to put the nonclinical findings into clinical perspective. Adjusting the body surface area exposure margins based on total daily dose alone would imply a greater safety margin, which would be inaccurate and misleading if the actual exposure with your product is comparable to the referenced drug product. For your eventual product labeling, you must take this into consideration and either propose adequate language that is scientifically accurate, clinically meaningful, and not misleading or provide actual exposure data to revise the safety margins. The latter may require animal toxicokinetic studies that mimic the dosing regimen employed in the studies cited in the referenced product labeling.*

- From 74-day filling communication letter issued on March 3, 2015:

*We note that the submitted study entitled “Computational assessment and evaluation of potential genotoxicity of three Meloxicam impurities using CASE Ultra” predicted that the drug product impurity (b) (4) was positive for bacterial mutagenicity and therefore the NDA indicated that this impurity would be kept within the acceptable intake of 1.5 mcg/day in accordance with the ICH M7 guideline: Assessment and Control of DNA Reactive (Mutagenic) Impurities In Pharmaceuticals to Limit Potential Carcinogenic Risk. However, the drug product specification for this impurity is NMT (b) (4) %, which could potentially result in daily exposures of (b) (4) mcg/day and (b) (4) mcg/day for the 5 mg and 10 mg tablets, respectively. You must either reduce the drug product specification to NMT 1.5 mcg/day or demonstrate that the impurity is negative in an Ames test.*

On April 7, 2015, the Applicant responded that the specification for drug impurity (b) (4) [meloxicam known related (b) (4)] was incorrectly stated as “NMT (b) (4) %”. The correct specification for this impurity is “NMT (b) (4) %”. Therefore, this impurity will be kept within the acceptable intake of NMT 1.5 mcg/day.

### **3 Studies Submitted**

The Applicant conducted an in silico computational genotoxicity evaluation of three known meloxicam related impurities in order to predict their genotoxic potential (see Section 7 Genetic Toxicology).

## 4 Pharmacology

No new pharmacology studies were submitted with this NDA.

## 5 Pharmacokinetics/ADME/Toxicokinetics

No new pharmacokinetics, ADME, or toxicokinetics studies were submitted with this NDA.

## 6 General Toxicology

No new general toxicology studies were submitted with this NDA.

## 7 Genetic Toxicology

### 7.1 In silico computational genotoxicity evaluation

<b>Study title: Computational assessment and evaluation of potential genotoxicity of 3 Meloxicam impurities using CASE Ultra</b>	
Study no.:	11540-21468
Study report location:	SD 1, eCTD 4.2.3.7.7.
Conducting laboratory and location:	(b) (4)
Final report date:	May 21, 2014
GLP compliance:	No

**Key finding:**

(b) (4) is positive for potential genotoxicity in humans due to the confirmation of a structural activity relationship by the in silico genetic toxicity models. The other two impurities are negative. The Applicant noted that the results generally are correct at an 80% probability level.

**Method:**

The mutagenicity assessment was performed with a computer based expert system, consisting of the CASE Ultra software and one set of designed expert models encompassing both rule-based and statistical-based prediction methodologies.

The genotoxic potential of the tested impurities were evaluated using a set of models developed from the FDA archives and public domain data containing results of the following assays: bacterial gene mutation, mammalian gene mutation in vitro, chromosomal aberrations in vitro, micronucleus in vivo.

**Results:****The results of tests with the genetic toxicity set**

Compound	ASSAY													
	AMES			MN <i>in vivo</i>			ML <i>in vitro</i>			CA <i>in vitro</i>				
	A7B	AT	ECOLI	A7S	A7T	A8J	A7N	AN7	AN8	A7U	A7V	A7W	A7X	A8H
(b) (4)	P	N		P	P	N	P	N	N	P	N	P	P	N
	N	N		N	P	N	N	N	N	N	N	N	N	NC
	N	N		N	N	N	N	N	N	N	N	N	N	P

AMES = bacterial mutation assay; ML = mouse lymphoma; CA = chromosomal aberration; MN = mouse micronucleus

P positive; N negative; NC = no call

**Summary of results and overall conclusions for the genotoxicity tests**

Compound	Ames	MN <i>in vivo</i>	CA <i>in vitro</i>	ML <i>in vitro</i>	FINAL CONCLUSION
	Review Expert	Review Expert	Review Expert	Review Expert	
(b) (4)	Positive	Positive	Positive	Negative	Positive
	Negative	Negative	Negative	Negative	Negative
	Negative	Negative	Negative	Negative	Negative

AMES = bacterial mutation assay; ML = mouse lymphoma; CA = chromosomal aberration; MN = mouse micronucleus

**Reviewer comments:**

The above results were confirmed by FDA/CDER/OTS/OCP/DARS for bacterial mutagenicity using (quantitative) structure-activity relationship [(Q)SAR] models (See Attachment 1).

**8 Carcinogenicity**

No new carcinogenicity studies were submitted with this NDA.

**9 Reproductive and Developmental Toxicology**

No new reproductive and developmental toxicology studies were submitted with this NDA.

**10 Special Toxicology Studies**

No new special toxicology studies were submitted with this NDA.

**11 Integrated Summary and Safety Evaluation**

See Executive Summary

**12 Attachments**

## Attachment 1

To: Armaghan Emami  
 cc: Dan Mellon  
 From: CDER/OTS/OCP/DARS: The Chemical Informatics Group  
 Re: NDA 207233  
 Date: June 9, 2015

### Summary

Three impurities identified in NDA 207233 for Meloxicam have been evaluated by CDER/OTS/OCP/DARS for bacterial mutagenicity using (quantitative) structure-activity relationship [(Q)SAR] models. Three software programs were used: *Derek Nexus* 4.1.0 (*DX*), *Leadscope Model Applier* 2.0.3-1 (*LMA*), and *CASE Ultra* 1.5.2.0 (*CU*). The (Q)SAR assessment of mutagenic potential is consistent with recommendations described in the ICH M7 guideline (i.e., using multiple complementary methodologies to predict the outcome of a bacterial mutation assay). The guideline also contains a provision for the application of expert knowledge to provide additional evidence on the relevance of (Q)SAR model predictions.

A (Q)SAR analysis was also performed by the sponsor using the statistical-based system *CU* 1.5.0.0, which is an older version of the current program used by the Chemical Informatics Group. The software generated a positive prediction for (b) (4). The two other impurities were predicted to be negative for bacterial mutation. The sponsor's (Q)SAR assessment uses only a single methodology, which is consistent with the ICH M7 guideline's implementation period recommendations. In order to confirm the results of the earlier version of *Case Ultra* and to provide additional weight to the predictions, the test compounds were run against the three software programs currently used for in-house consultations.

Based on the entire weight of evidence, (b) (4) is predicted to be positive for bacterial mutagenicity. (b) (4) are predicted to be negative for bacterial mutagenicity.

Chemical 1: (b) (4)

### Bacterial Mutagenicity (Q)SAR Predictions<sup>1</sup>

(b) (4)	Software	Salmonella Mutagenicity	TA102/E.coli Mutagenicity
	<i>Derek Nexus</i>	+	+
	<i>Leadscope Model Applier</i>	NC	Eqv
	<i>CASE Ultra</i>	-	-
	Overall Software Prediction	+	+
	Overall Expert Prediction	+	+

(b) (4) is predicted to be positive for bacterial mutagenicity by *DX*. The prediction is based on the presence of (b) (4) (shown below). Alert details are provided in the Appendix.



<sup>1</sup> + = positive; - = negative; Eqv = equivocal; NC = test chemical features are not adequately represented in the model training data set, leading to a no call.

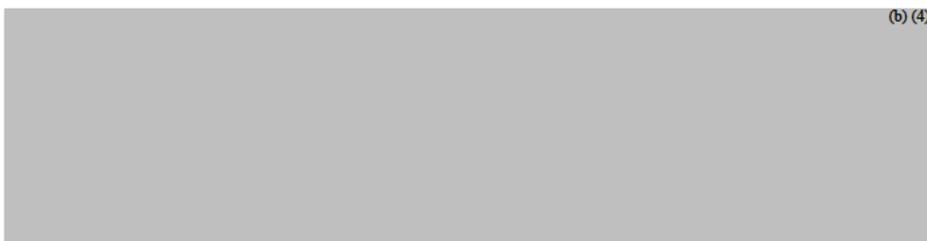
Note that the European Chemicals Agency (ECHA) website provides the following summary conclusion for Ames testing with (b) (4) in *Salmonella* strains TA98, TA100, TA102, TA1535, and TA1537.

"It is concluded that (b) (4) is clearly negative in 3 strains of *S. typhimurium* whereas a weak mutagenic response in 2 other genotypically different strains could not be ruled out definitely. A mutagenic risk is unlikely because of the marginal response and the required high concentrations."

Because detailed methodology and data are not available, it is not possible to draw a definitive conclusion regarding the experimental result.

Comparison of CU Predictions

The negative prediction in CU v1.5.2.0 conflicts with the Sponsor's previous analysis using CU v1.5.0.0. The positive v1.5.0.0 prediction is based on the presence of alerting fragment (b) (4). This fragment is associated with the (b) (4) moiety and is derived from 2 training set molecules (structures shown below). CU v1.5.2.0 also identified alert (b) (4) derived from the same 2 molecules. However, a revision in the CU algorithm results in less weight being given to (b) (4) because the structure also contains a (b) (4). As a consequence, the CU prediction is downgraded to negative. Given the small number of relevant training set molecules the model does not sufficiently cover the (b) (4).



Reference:  
ECHA website



Chemical 2: (b) (4)

Bacterial Mutagenicity (Q)SAR Predictions<sup>1</sup>

(b) (4)	Software	<i>Salmonella</i> Mutagenicity	<i>TA102/E.coli</i> Mutagenicity
	<i>Derek Nexus</i>	-	-
	<i>Leadscope Model Applier</i>	-	-
	<i>CASE Ultra</i>	Eqv	-
	Overall Software Prediction	-	-
	Overall Expert Prediction	-	-

(b) (4) is predicted to be negative for bacterial mutagenicity (i.e., both *Salmonella* and *E.coli/TA102* mutagenicity).

Chemical 3:

(b) (4)

(b) (4)

**Bacterial Mutagenicity (Q)SAR Predictions<sup>1</sup>**

(b) (4)	Software	<i>Salmonella</i> Mutagenicity	TA102/ <i>E.coli</i> Mutagenicity
	<i>Derek Nexus</i>	-	-
	<i>Leadscope Model Applier</i>	-	-
	<i>CASE Ultra</i>	-	-
	Overall Software Prediction	-	-
	Overall Expert Prediction	-	-

(b) (4)

is predicted to be negative for bacterial mutagenicity (i.e., both *Salmonella* and *E.coli*/TA102 mutagenicity).

**Appendix**

(b) (4)

**Mechanism:** The (b) (4) was activated by the compound with *DX* reporting that (b) (4) (b) (4) have been shown to exhibit mutagenic activity in the Ames *Salmonella* test with enhanced mutagenicity in TA98 and TA100 in the presence of S9 activation. The mechanism of action is generally considered to involve (b) (4) typically mediated by (b) (4) and subsequent (b) (4). The resulting (b) (4) product may then give rise to a reactive (b) (4) which is capable of binding to cellular nucleophiles such as DNA (b) (4).

**Positive Predictivity:** Twenty-three compounds from an FDA CFSAN data set possess this alert of which 21 (91%) are reported as positive.

This report has been reviewed and approved by CDER/OTS/OCP/DARS.

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/s/  
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ARMAGHAN EMAMI  
08/31/2015

JAY H CHANG  
08/31/2015

RICHARD D MELLON  
08/31/2015

I concur with Dr. Emami and Chang's recommendation that NDA 207233 may be approved from the nonclinical pharmacology toxicology perspective.

**PHARMACOLOGY/TOXICOLOGY NDA FILEABILITY CHECKLIST**

**NDA Number:** 207233

**Applicant:** Iroko Pharm    **Stamp Date:** 12/23/14

**Drug Name:** Vivlodex

**NDA/BLA Type:** 505(b2)    **DAAAP/OND/CDER/FDA**

On **initial** overview of the NDA application for Refuse to File (RTF):

	<b>Parameters</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
1	On its face, is the pharmacology section of the NDA organized (in accord with 21 CFR 314 and current guidelines for format and content) in a manner to allow substantive review to begin?	+		
2	Is the pharmacology/toxicology section of the NDA indexed and paginated in a manner allowing substantive review to begin?	+		
3	On its face, is the pharmacology/toxicology section of the NDA legible so that substantive review can begin?	+		
4	Are all required (*) and requested BBIND studies (in accord with 505(b1) and (b2) including referenced literature) completed and submitted in this NDA (carcinogenicity*, mutagenicity*, teratogenicity*, effects on fertility*, juvenile studies, acute and repeat dose adult animal studies*, maximum tolerated dose determination, dermal irritancy, ocular irritancy, photo co-carcinogenicity, animal pharmacokinetic studies, safety pharmacology, etc)?			N/A
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies been conducted with the appropriate formulation?			N/A
6	Is (are) the excipient(s) appropriately qualified (including interaction between the excipients if			N/A

	applicable)?			
7	On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the sponsor <u>submitted</u> a rationale to justify the alternative route?			N/A
8	Has the sponsor <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?			N/A
9	Has the sponsor submitted all special studies/ data requested by the Division during pre-submission discussions with the sponsor?			N/A
10	Are the proposed labeling sections relative to pharmacology, reproductive toxicology, and carcinogenicity appropriate (including human dose multiples expressed in either mg/m <sup>2</sup> or comparative serum/plasma levels) and in accordance with 201.57?		+	We note that due to increased bioavailability with the drug product, the total daily dose is lower than the referenced drug product yet provides comparable exposure levels. Most of the nonclinical data in the referenced drug product labeling includes exposure margins that are based on body surface extrapolations. Exposure margins are necessary to put the nonclinical findings into clinical perspective. Adjusting the body surface area exposure margins based on total daily dose alone would imply a greater safety margin, which would be inaccurate and misleading if the actual exposure with your product is comparable to the referenced drug product. We have asked the Sponsor take this into consideration and either propose adequate language that is scientifically accurate, clinically meaningful, and not misleading or provide actual exposure data to revise the safety margins. The Sponsor has not changed the label accordingly.

11	Has the sponsor submitted any toxicity data to address impurities, new excipients, leachables, etc. issues.	+		Computational assessment and evaluation of potential genotoxicity of three Meloxicam impurities using CASE Ultra has been conducted.
12	Has the sponsor addressed any abuse potential issues in the submission?			N/A
13	If this NDA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A
14	From a pharmacology/ toxicology perspective, is the NDA fileable? If ``no`` please state below why it is not.	+		

**IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes**

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

**Comments to Sponsor:**

We note that the submitted study entitled “Computational assessment and evaluation of potential genotoxicity of three Meloxicam impurities using CASE Ultra” predicted that the drug product impurity (b) (4) was positive for bacterial mutagenicity and therefore the NDA indicated that this impurity would be kept within the acceptable intake of 1.5 mcg/day in accordance with the ICH M7 guideline: *Assessment and Control of DNA Reactive (Mutagenic) Impurities In Pharmaceuticals to Limit Potential Carcinogenic Risk*. However, the drug product specification for this impurity is NMT (b) (4)%, which could potentially result in daily exposures of (b) (4) mcg/day and (b) (4) mcg/day for the 5 mg and 10 mg tablets, respectively. You must either reduce the drug product specification to NMT 1.5 mcg/day or demonstrate that the impurity is negative in an Ames test.

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/s/  
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ARMAGHAN EMAMI  
02/04/2015

JAY H CHANG  
02/08/2015

RICHARD D MELLON  
02/09/2015