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APPLICATION NUMBER:

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NON-CLINICAL REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	211210
Supporting document/s:	1, 24 (labeling)
Applicant's letter date:	December 21, 2017 September 12, 2018
Product:	TRADENAME Meloxicam Orally Disintegrating Tablet (ODT), 7.5 mg and 15 mg
Indication:	Relief of the signs and symptoms of: • Osteoarthritis (OA); • Rheumatoid arthritis (RA) • Pauci-articular or polyarticular course juvenile rheumatoid arthritis (JRA) in patients who weigh ≥60 kg
Applicant:	TerSera Therapeutics LLC
Review Division:	Division of Anesthesia, Analgesia, and Addiction Products
Reviewer:	Armaghan Emami, PhD
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Template Version: September 1, 2010

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1 Executive Summary

1.1 Introduction

NDA 211210 was submitted by the Applicant, TerSera Therapeutics LLC, on December 21, 2017 for marketing approval of TRADENAME Meloxicam Orally Disintegrating Tablet (ODT) as a 505(b)(2) application relying on the Agency's previous determination of safety and efficacy of the listed drug Mobic® tablets (NDA 20938; Boehringer Ingelheim, approved on April 13, 2000), the scientific literature, and Applicant-conducted studies (under IND 104140). TRADENAME Meloxicam ODT contains meloxicam, a non-steroidal anti-inflammatory drug (NSAID), and the proposed indications include the relief of the signs and symptoms of osteoarthritis (OA), rheumatoid arthritis (RA), and pauci-articular or polyarticular course juvenile rheumatoid arthritis (JRA) in patients who weigh ≥60 kg, which are identical to the listed drug Mobic. TRADENAME Meloxicam ODT is a freeze dried orally administered formulation and is designed to rapidly disintegrate in the mouth. TRADENAME Meloxicam ODT will be available as 7.5 mg and 15 mg tablets and will be administered as one tablet once daily, which is the identical to the listed drug Mobic.

1.2 Brief Discussion of Nonclinical Findings

The TRADENAME Meloxicam ODT nonclinical program was based on the safety profile of Mobic and on the published pharmacology, PK, and toxicology literature. There are no novel excipients in the drug product and no impurities or degradation products in the meloxicam drug substance and drug product that exceed ICH regulatory thresholds. Therefore, additional nonclinical studies were not required to support the safety of this drug product formulation. From a pharmacology toxicology perspective, the NDA may be approved.

1.3 Recommendations

1.3.1 Approvability

From a nonclinical pharmacology toxicology perspective, NDA 211210 may be approved with the recommended labeling revisions.

1.3.2 Additional Non-Clinical Recommendations

None

1.3.3 Labeling

Table below summarizes this reviewer's comments on the Sponsor's proposed language and highlights specific issues that will need to be addressed. The final label will be based on further internal discussion and negotiations with the Applicant.

Mobic Label (2016)	**Applicant's Proposed Labeling**	**Reviewer's Proposed Labeling**	**Comments and Rationale for Reviewer's Proposed Labeling Language**
8.1 Pregnancy	**8.1 Pregnancy**	**8.1 Pregnancy**	
Risk Summary Use of NSAIDs, including MOBIC, during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including MOBIC, in pregnant women starting at 30 weeks of gestation (third trimester) [see Warnings and Precautions (5.10)].	*Risk Summary* Use of NSAIDs, including QMIIZ ODT, during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including QMIIZ ODT, in pregnant women starting at 30 weeks of (b) (4) (third trimester) [see Warnings and Precautions (5.10)].	*Risk Summary* Use of NSAIDs, including TRADENAME Meloxicam ODT, during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including TRADENAME Meloxicam ODT, in pregnant women starting at 30 weeks of (b) (4) (third trimester) [see Warnings and Precautions (5.10)].	This is consistent with MOBIC labeling. The proposed tradename (b) (4) was under review by DMEPA at the time of this review. Refer to the final approved name in the action letter.
There are no adequate and well-controlled studies of MOBIC 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.	There are no adequate and well-controlled studies of QMIIZ ODT 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. (b) (4)	There are no adequate and well-controlled studies of TRADENAME Meloxicam ODT 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.	We defer to clinical review team and maternal health team (MHT) for the human risk summary statement. Moved to the end of the risk summary
In animal reproduction studies, embryofetal death was observed in rats and rabbits treated during the period of organogenesis with meloxicam at oral doses equivalent to 0.65- and 6.5-times the maximum recommended human dose (MRHD) of MOBIC.	In animal reproduction studies, embryofetal death was observed in rats and rabbits treated during the period of organogenesis with meloxicam at oral doses equivalent to 0.65- and 6.5-times the maximum recommended human dose (MRHD) of QMIIZ ODT.	In animal reproduction studies, embryofetal death was observed in rats and rabbits treated during the period of organogenesis with meloxicam at oral doses equivalent to 0.65- and 6.5-times the maximum recommended human dose (MRHD) of TRADENAME Meloxicam ODT.	
	No teratogenic effects were observed in rats and rabbits treated with meloxicam during organogenesis at an oral dose equivalent to 2.6 and 26-times the MRHD (b) (4)	No teratogenic effects were observed in rats and rabbits treated with meloxicam during organogenesis at an oral dose equivalent to 2.6 and 26-times the MRHD.	This paragraph is moved from latest paragraph in Mobic to be consistent with the referenced product label.
Increased incidence of	An increased incidence of	An increased incidence of septal heart defects were	The Applicant submitted a literature review

septal heart defects were observed in rabbits treated throughout embryogenesis with meloxicam at an oral dose equivalent to 78-times the MRHD.	septal heart defects were observed in rabbits treated throughout embryogenesis with meloxicam at an oral dose equivalent to 78-times the MRHD. (b) (4) [redacted]	observed in rabbits treated throughout embryogenesis with meloxicam at an oral dose equivalent to 78-times the MRHD.	summarizing published nonclinical studies that investigated effects of meloxicam on reproduction, development, and fertility. The Applicant propose to add new information to the label. (b) (4) [redacted] this reviewer does not consider it appropriate to include this information in the TRADENAME Meloxicam ODT label at this time.
In pre- and post-natal reproduction studies, there was an increased incidence of dystocia, delayed parturition, and decreased offspring survival at 0.08-times MRHD of meloxicam. No teratogenic effects were observed in rats and rabbits treated with meloxicam during organogenesis at an oral dose equivalent to 2.6 and 26-times the MRHD [see Data].	In pre- and post-natal reproduction studies, there was an increased incidence of dystocia, delayed parturition, and decreased offspring survival at 0.08-times MRHD of meloxicam.	In pre- and post-natal reproduction studies, there was an increased incidence of dystocia, delayed parturition, and decreased offspring survival at 0.08-times MRHD of meloxicam [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.	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.	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.	NSAID class labeling language.
		The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. 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.	Standard PLLR data

Data Animal Data Meloxicam was not teratogenic when administered to pregnant rats during fetal organogenesis at oral doses up to 4 mg/kg/day (2.6-fold greater than the MRHD of 15 mg of MOBIC based on 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 (78-fold greater than the MRHD based on BSA comparison). The no effect level was 20 mg/kg/day (26-fold greater than the MRHD based on BSA conversion).	Data *Animal Data* Meloxicam was not teratogenic when administered to pregnant rats during fetal organogenesis at oral doses up to 4 mg/kg/day (2.6-fold greater than the MRHD of 15 mg of QMIIZ ODT based on 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 (78-fold greater than the MRHD based on BSA comparison). The no effect level was 20 mg/kg/day (26-fold greater than the MRHD based on BSA conversion).	*Data* *Animal Data* Meloxicam was not teratogenic when administered to pregnant rats during fetal organogenesis at oral doses up to 4 mg/kg/day (2.6-fold greater than the MRHD of 15 mg of TRADENAME Meloxicam ODT based on 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 (78-fold greater than the MRHD based on BSA comparison). The no effect level was 20 mg/kg/day (26-fold greater than the MRHD based on BSA conversion).	This is consistent with MOBIC labeling.
	(b) (4) [redacted]		As discussed above, this reviewer does not consider it appropriate to include this information in the TRADENAME Meloxicam ODT label at this time
In rats and rabbits, embryolethality occurred at oral meloxicam doses of 1 mg/kg/day and 5 mg/kg/day, respectively (0.65and 6.5-fold greater, respectively, than the MRHD based on BSA comparison) when administered throughout organogenesis.	In rats and rabbits, embryolethality occurred at oral meloxicam 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 comparison) when administered throughout organogenesis.	In rats and rabbits, embryolethality occurred at oral meloxicam 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 comparison) when administered throughout organogenesis.	
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 (0.08-	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 (0.08-times MRHD based on BSA	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 (0.08-times MRHD based on BSA	

times MRHD based on BSA comparison).	comparison).	comparison).	
8.2 Lactation <u>Risk Summary</u> There are no human data available on whether meloxicam is present in human milk, or on the effects on breastfed infants, or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for MOBIC and any potential adverse effects on the breastfed infant from the MOBIC or from the underlying maternal condition. <u>Data</u> <u>Animal Data</u> Meloxicam was present in the milk of lactating rats at concentrations higher than those in plasma.	**8.2 Lactation** <u>Risk Summary</u> There are no human data available on whether meloxicam is present in human milk, or on the effects on breastfed infants, or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for QMIIZ ODT and any potential adverse effects on the breastfed infant from the QMIIZ ODT or from the underlying maternal condition. (b) (4) [redacted] Meloxicam was present in the milk of lactating rats at concentrations higher than those in plasma. The ratio of the concentration of meloxicam in milk versus plasma ranged from 0.77 at 1 hour postdose to 1.66 at 24-hours post dose.	**8.2 Lactation** <u>Risk Summary</u> There are no human data available on whether meloxicam is present in human milk, or on the effects on breastfed infants, or on milk production. Meloxicam was present in the milk of lactating rats at concentrations higher than those in plasma. The concentration of the drug in animal milk does not necessarily predict the concentration of drug in human milk. However, when a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRADENAME Meloxicam ODT and any potential adverse effects on the breastfed infant from the TRADENAME Meloxicam ODT or from the underlying maternal condition.	The Lactation Risk Summary language was recommended by MHT. We defer to the MHT and the clinical review team on lactation language The proposed additional sentence (b) (4) [redacted] will be removed as it is not clear (b) (4) [redacted].
8.3 Females and Males of Reproductive Potential *<u>Infertility</u>* *<u>Females</u>* Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including MOBIC, 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 have also shown a reversible delay in ovulation. Consider	**8.3 Females and Males of Reproductive Potential** *<u>Infertility</u>* *<u>Females</u>* Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including QMIIZ ODT, 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 have also shown a reversible delay in ovulation. Consider	**8.3 Females and Males of Reproductive Potential** *<u>Infertility</u>* *<u>Females</u>* Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including TRADENAME Meloxicam ODT, 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 have also shown a reversible delay in	

withdrawal of NSAIDs, including MOBIC, in women who have difficulties conceiving or who are undergoing investigation of infertility.	withdrawal of NSAIDs, including QMIIZ ODT, in women who have difficulties conceiving or who are undergoing investigation of infertility.	ovulation. Consider withdrawal of NSAIDs, including TRADENAME Meloxicam ODT, in women who have difficulties conceiving or who are undergoing investigation of infertility. *Males* In a published study, oral administration of meloxicam to male rats for 35 days resulted in decreased sperm count and motility and histopathological evidence of testicular degeneration [*See 13.1 Impairment of Fertility*].	Data Source: Uzun et al. (2015)
12.1 Mechanism of Action Meloxicam has analgesic, anti-inflammatory, and antipyretic properties. The mechanism of action of MOBIC, like that of other NSAIDs, is not completely understood but involves inhibition of cyclooxygenase (COX-1 and COX-2). Meloxicam is a potent inhibitor of prostaglandin s nthesis *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. Because meloxicam is an inhibitor of prostaglandin s nthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues. **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** <u>*Carcinogenesis*</u> There was no increase in tumor incidence in long-term carcinogenicity studies in	**12.1 Mechanism of Action** Meloxicam has analgesic, anti-inflammatory, and antipyretic properties. The mechanism of action of QMIIZ ODT, like that of other NSAIDs, is not completely understood but involves inhibition of cyclooxygenase (COX-1 and COX-2). 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. Because meloxicam is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues. **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** <u>*Carcinogenesis*</u> There was no increase in tumor incidence in long-term carcinogenicity studies in	**12.1 Mechanism of Action** Meloxicam has analgesic, anti-inflammatory, and antipyretic properties. The mechanism of action of TRADENAME Meloxicam ODT, like that of other NSAIDs, is not completely understood but involves inhibition of cyclooxygenase (COX-1 and COX-2). 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. Because meloxicam is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues. **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** <u>*Carcinogenesis*</u> There was no increase in tumor incidence in long-term carcinogenicity studies in	This is consistent with MOBIC labeling. This is consistent with MOBIC labeling.

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 0.5-and 2.6-times, respectively, the maximum recommended human dose [MRHD] of 15 mg/day MOBIC based on body surface area [BSA] comparison). *Mutagenesis* 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. *Impairment of Fertility* Meloxicam did not impair male and female fertility in rats at oral doses up to 9 mg/kg/day in males and 5 mg/kg/day in females (up to 5.8- and 3.2-times greater, respectively, than the MRHD based on BSA comparison).	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 0.5-and 2.6-times, respectively, the maximum recommended human dose [MRHD] of 15 mg/day QMIIZ ODT based on body surface area [BSA] comparison). *Mutagenesis* 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. *Impairment of Fertility* Meloxicam did not impair male and female fertility in rats at oral doses up to 9 mg/kg/day in males and 5 mg/kg/day in females (up to 5.8- and 3.2-times greater, respectively, than the MRHD based on BSA comparison).	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 0.5-and 2.6-times, respectively, the maximum recommended human dose [MRHD] of 15 mg/day TRADENAME Meloxicam ODT based on body surface area [BSA] comparison). *Mutagenesis* 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. *Impairment of Fertility* Meloxicam did not impair male and female fertility in rats at oral doses up to 9 mg/kg/day in males and 5 mg/kg/day in females (up to 5.8- and 3.2-times greater, respectively, than the MRHD based on BSA comparison). In a published study, oral administration of 1 mg/kg (0.6x the maximum human daily dose) meloxicam to male rats for 35 days resulted in decreased sperm count and motility and histopathological evidence of testicular degeneration.	Data Source: Uzun et al. (2015)

A comprehensive literature search was conducted to supplement nonclinical information available in the Mobic Product Label. The search period was 01 January 2000 to 30 June 2017.

A total of 4 new nonclinical in vitro pharmacokinetic literature references and 12 new nonclinical toxicity references were identified as potentially relevant by the Applicant. For the pharmacokinetics references see Dr. Kwatra's clinical pharmacy review.

A review of the nonclinical toxicity published literature was provided. Three published studies t included information about the toxicity of repeated doses of meloxicam in rats (Inal et al. 2014, Pehlivan et al. 2010, and Burukoglu et al. 2016). Overall, these studies did not provide new data or information about new toxicities that impact the safety profile established for meloxicam. Nine published studies assessed the effects of meloxicam on reproductive parameters in male rats and in female rats, rabbits, and nonhuman primates (cynomolgus monkeys) (Uzun et al. 2015, Jaffal et al. 2006, Paksoy and Kirbas 2017, Salhab et al. 2001, Salhab et al. 2003, Hester et al. 2010, McCann et al. 2013). Among these studies, the results of Uzun et al (2015) should be considered for inclusion in labeling (Section 8.3 and 13.1). for more detail see section 9 of this review. In addition, several published studies examined the effects of meloxicam on embryo-fetal development in mice, rats, and rabbits (Thaete et al. 2013, Cappon et al. 2003). These studies report similar findings to what is already in the current labeling.

2 Drug Information

2.1 Drug

CAS Registry Number: 71125-38-7

Generic Name: Meloxicam ODT

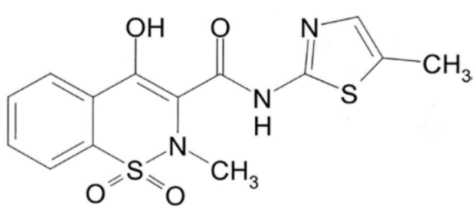
Code Name: Melox 00 (3526900)

Chemical Name: 4-hydroxy-2-methyl-N-(5-methyl-1,3-thiazolyl-2-yl)-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide

Molecular Formula: $C_{14}H_{13}N_3O_4S_2$

Molecular Weight: 351.4 g/mol

Structure or Biochemical Description:



Pharmacologic Class: Nonsteroidal anti-inflammatory drug (NSAID)

2.2 Relevant INDs, NDAs, BLAs and DMFs

Meloxicam was developed under IND 104140. The only referenced drug product for this 505(b)(2) application is NDA 20938 (Mobic).

Application	*Drug Name*	*Route*	*Strength*	*Status/Date*	*Indication*
NDA 20938	Mobic	Oral	7.5 and 15 mg tablets	Approved 4/13/2000	Chronic pain
IND 104140	Meloxicam (b) (4)	Oral	7.5 and 15 mg tablest	Active 12/20/2009	Relief of Signs and Symptoms of Osteoarthritis and Rheumatoid Arthritis

DMF	Subject	Holder	Status	Comment
[redacted] (b) (4)			Active 09/30/2010	Not formally reviewed. A letter of authorization from [redacted] (b) (4) was provided by the Applicant to access the DMF
			Active 10/08/2003	Reviewed on November 29, 2010 (Referenced for NDA [redacted] (b) (4))

2.3 Drug Formulation

TRADENAME Meloxicam ODT is a freeze dried orally administered formulation containing 7.5 mg or 15 mg meloxicam and is designed to rapidly disintegrate in the mouth. Both strengths of meloxicam are orange flavored, yellow, circular tablets and debossed with an identifying logo.

Drug product composition

Composition of Meloxicam Orally Disintegrating Tablet

Name of Ingredient	Quantity per 7.5 mg tablet (mg)	Quantity per 15 mg tablet (mg)	Function	Reference to Standards
Active Ingredient				
Meloxicam	7.5	15.0	Active Ingredient	USP
Other Ingredients				
Gelatin	[redacted] (b) (4)			USP NF
Mannitol				USP
Citric Acid, [redacted] (b) (4)				USP
Aspartame[1]				USP NF
Orange flavor [redacted] (b) (4)				In-House
				[redacted] (b) (4)

[1] Amount of phenylalanine (a component of aspartame) is 0.30 mg for the 7.5 mg dose and 0.59 mg for the 15 mg dose.

[redacted] (b) (4)

2.4 Comments on Novel Excipients

All inactive ingredients are within maximum potency levels listed in the FDA Inactive Ingredient Database (IID) for the oral route.

- <u>Gelatin:</u> The total daily intake (TDI) is 12 mg based on the maximum recommended daily dose (MRDD) of 15 mg of Meloxicam ODT. This excipient is listed in the FDA Inactive Ingredient Database (IID) with a max potency of 260.85 mg for the oral route. Therefore, this excipient is covered for both local and systemic safety.

- Mannitol: The TDI is 9 mg based on the MRDD of Meloxicam ODT. This excipient is listed in the FDA IID with a max potency of 1196 mg for the oral route. Therefore, this excipient is covered for both local and systemic safety.
- Aspartame: The TDI is 1.05 mg based on the MRDD of Meloxicam ODT. This excipient is listed in the FDA IID with a max potency of 450 mg for the oral route. Therefore, this excipient is covered for both local and systemic safety.
- Flavor Orange [redacted] (b) (4): The TDI is 1.5 mg based on the MRDD of 15 mg of Meloxicam ODT. This excipient is listed in the FDA IID with a max potency of up to 50 mg for the oral route. However, the product with 50 mg orange flavor is approved for an acute indication. There is another product approved for chronic oral use (seizure) with a TDI of 192 mg. Therefore, this excipient is covered for both local and systemic safety for a chronic indication.

2.5 Comments on Impurities/Degradants of Concern

All impurities are within the ICH Q3A(R2) levels for the drug substance and ICH Q3B(R2) levels for the drug product.

Drug Substance Impurities

The following impurities could potentially arise from the meloxicam manufacturing process used by [redacted] (b) (4) (DMF [redacted] (b) (4)). The structures and chemical names are given in table below.

Chemical Structures for the Related Impurities

Impurity Name	Chemical Name	Structure

(b) (4)

For a drug substance with a maximum daily dose of 15 mg, the Q3A(R2) qualification threshold is NMT (b) (4) % (b) (4) whichever is lower. All impurities are within ICH Q3A(R2) identification and qualification thresholds as shown in the Applicant's table below.

Incoming Release Specification for Meloxicam Drug Substance at Catalent Swindon

Test parameter	Acceptance Criteria	Method
Appearance	A pale yellow crystalline powder	Visual
Identification A, B	Must be positive	A- IR, USP <197K> B-The retention time of the meloxicam peak of the Sample solution corresponds to that of the Standard solution, as obtained in the Assay
Loss on drying	Not more than (b) (4) [redacted] %w/w	USP <731>
Residue on ignition	Not more than [redacted] %w/w	USP <281>
Related Substances[1]: (b) (4) [redacted] Other known impurities Individual unknown impurities Total Impurities	 Not more than (b) (4) [redacted] % Not more than [redacted] % Not more than [redacted] 5% Not more than [redacted] % Not more than [redacted] %	USP<621> Test 1
Assay	(b) (4) [redacted] % calculated (b) (4) [redacted]	USP<621>
Residual Solvents[2]	Meets the requirements of the USP	USP <467> (b) (4) [redacted]
Particle size[3]	D (b) (4) [redacted] µm	Laser diffraction. See Section 3.2.S.4.2.1.

IR = infrared; USP = United States Pharmacopeia
[1] See Section 3.2.S.3.2 for structure of related compounds A and B
[2] See Section 3.2.S.4.5 for further information regarding residual solvents testing
[3] This test is performed by the drug substance manufacturer and results will be taken from drug substance manufacturer Certificate of Analysis.

<u>Residual Solvents</u>

The NDA noted that the following solvents are used in the meloxicam manufacturing process, and added that (b) (4) [redacted] is a possible impurity of the solvents.

(b) (4) [redacted]

The Applicant justified that specifications for residual solvents were not needed with the following rationale:

> According to ICH Q3C guideline requirements, the capability of the validated manufacturing process is verified (b) (4) [redacted]

According the CMC review on the drug substance by Dr. Friedrich Burnett, the proposed control of materials, reagents, solvents with respect to the Drug Substance is adequate. Refer to Dr. Burnett's review for more details regarding the acceptability of the Applicant's approach. There are no additional concerns regarding residual solvents from the nonclinical perspective.

Elemental Impurities

According to the CMC drug substance review, the DMF Holder performed a risk assessment and provided sufficient justification to delete Heavy Metals from the Specifications. The information was considered adequate, and no change was required from the Applicant. Therefore, there are no additional safety concerns regarding elemental impurities in the drug substance from the nonclinical perspective.

Drug Product Degradants

The proposed specifications for Meloxicam Orally Disintegrating Tablet drug product are presented in the table below.

Specification for Meloxicam Orally Disintegrating Tablets

Test parameter	Acceptance Criteria	Method
Appearance	Yellow, circular, freeze-dried tablets debossed with an identifying logo[1]. The tablets must be sufficiently robust to be removed from the packaging without breaking.	Visual examination AM253
Appearance of packaging	Shipper labels- Labels contain product name, Catalent batch number and expiry date Blisters- Blisters include product name, strength, Catalent batch number	Visual inspection
Identification (HPLC with UV detection)	For positive identification: The retention time of the Meloxicam peak in the sample chromatogram must be comparable to that of the Meloxicam peak in the nearest standard injection.	In house HPLC AM718
	For positive identification: The UV spectrum of the primary peak in the sample chromatogram must be comparable to that of the UV spectrum of the primary peak in the nearest standard injection.	
Assay	(b) (4) % label claim	In house HPLC AM718
Uniformity of dosage units by content uniformity	Complies with USP <905> requirements, AV ≤ (b) (4)	In house HPLC AM723 USP <905>, Content Uniformity
Disintegration	Not more than (b) (4) seconds for each of six tablets	In-House AM 059 (based on USP <701>)
		(b) (4)
Related Substances: Meloxicam Related Compound B Individual Unknown Degradation Product Total Degradation Products	 Not more than (b) (4) % Not more than (b) (4) % Not more than %	In house HPLC AM718
Microbiological purity: Total aerobic microbial count: TAMC Total yeasts and mould count: TYMC	 Not more than (b) (4) cfu/g Not more than cfu/g	USP <61>
Absence of pathogens: *Escherichia coli*	 Absent in 1 g	USP <62>
		(b) (4)

CFU = colony forming unity; HPLC = high-performance liquid chromatography; TAMC = total aerobic microbial count; TYMC = total yeast and molds count; USP = United States Pharmacopeia; UV = ultraviolet

For a drug product with a maximum daily dose of 15 mg, the appropriate ICH Q3B(R2) qualification threshold is NMT [redacted] (b) (4) % [redacted] (b) (4) whichever is lower. Of the four potential related compounds in the meloxicam drug substance, [redacted] (b) (4) potential degradation product found in Meloxicam ODT drug product. The proposed specifications for DP degradants are within the appropriate ICH Q3B(R2) qualification and identification thresholds. Also, no potential degradation products have been found in the stability batches.

<u>Residual Solvents</u>
The NDA noted "There are no solvents used in the manufacturing process of Meloxicam Orally Disintegrating Tablets and therefore no further testing is required in the drug product specification. This is acceptable.

<u>Elemental impurities</u>
No specifications were proposed for heavy metals. The Applicant provided a risk assessment using the Option 2a approach in accordance with ICH Q3D document *Elemental Impurities*. The Applicant provided the following rationale:

> Option 2a has been utilized to calculate common permitted concentration limits for the drug product components. Information on elemental impurities in the API and excipients provided by the suppliers has been reviewed against the option 2a calculated limits. All materials used in the manufacture of the Meloxicam products comply with the option 2a limits. The levels of elemental impurities in the Meloxicam products comply with the ICH Q3D requirements. No further assessment is required.

We consulted the CMC review team, and the drug product and process reviewers concluded that the Applicant's approach is acceptable. Therefore, there are no additional concerns regarding elemental impurities from the nonclinical perspective.

2.6 Proposed Clinical Population and Dosing Regimen

The proposed indication for TRADENAME Meloxicam ODT is the relief of the signs and symptoms of osteoarthritis (OA), rheumatoid arthritis (RA), and pauci-articular or polyarticular course juvenile rheumatoid arthritis (JRA) in patients who weigh ≥ 60 kg. The to-be-marketed oral doses are 7.5 and 15 mg once daily, which are the same as the referenced drug, Mobic.

2.7 Regulatory Background

Initially the IND 104140 was submitted by Wilmington on December 20, 2009. Then was transferred to TerSera on December 23, 2016. NDA 211210 was submitted on December 21, 2017 and the NDA was fileable from pharmacology/toxicology perspective with no comments for 74-day letter.

3 Studies Submitted

No new nonclinical studies were conducted with TRADENAME Meloxicam ODT and none were required.

4 Pharmacology

No new nonclinical pharmacology studies were conducted or required.

5 Pharmacokinetics/ADME/Toxicokinetics

No new ADME or other pharmacokinetic drug interaction studies for Meloxicam ODT were conducted or required**.**

6 General Toxicology

No new toxicology studies were submitted with this NDA. However, the Applicant provided a review of the published literature of 3 studies that included information about the toxicity of repeated doses of meloxicam in rats (Pahlivan et al., 2010, Inal et al., 2014, Burukoglu et al., 2016). According to the Applicant, overall, these studies did not provide new data or information about new toxicities that impact the safety profile established for meloxicam. These studies are summarized below. Tabulated summary of these studies was provided by the Sponsor (Appendix 1)

1. ***(Inal et al., 2014) Comparison of the effects of dexketoprofen trometamol, meloxicam and diclofenac sodium on fibular fracture healing, kidney and liver: an experimental rat model.***

In this study, male Sprague-Dawley rats were divided into 4 groups (N=7/group). Closed diaphyseal fractures were formed in the lest fibulas of all the rats. The NSAIDs dexketoprofen trometamol (DEXT), meloxicam (MEL) and diclofenac sodium (DIC) were intramuscularly administered to Groups I, II, and III, respectively, for a period of 10 days after the fibular fractures were performed. No agents were administered to Group IV (Control group). The rats were sacrificed on Day 28. The histopathological findings were compared.

Group I: DEXT, 0.98 mg/kg per half-day
Group II: MEL, 0.2 mg/kg per day
Group III: DIC; 1 mg/kg per day
Group IV: Control (No injection)

Key findings:

- DEXT and MEL impair the healing of bone fractures and that DIC does not histopathologically affect the healing process of bone fractures.
- DEXT, MEL, and DIC impaired the renal histopathology compared with the control group.

- The liver histopathological analysis showed that DEXT and MEL caused a higher degree of parenchymal necrosis compared with DIC.

Table 2
The descriptive data of the mean values, standard deviations and *p* values related to fibular fracture healing and bone marrow histopathology.

Histologic score			Bone marrow cellularity (the area near the callus)			Bone marrow cellularity (callus area)			Bone marrow cellularity (mean)		
Groups	*N*	Mean ± S.D.	Groups	*N*	Mean ± S.D.	Groups	*N*	Mean ± S.D.	Groups	*N*	Mean ± S.D.
DEXT	7	7.14 ± 0.69	DEXT	7	57.14 ± 22.14	DEXT	7	74.28 ± 18.12	DEXT	7	65.71 ± 19.66
MEL	7	6.14 ± 0.37	MEL	7	50.00 ± 20.81	MEL	7	84.28 ± 16.18	MEL	7	67.14 ± 16.03
DIC	7	7.85 ± 0.37	DIC	7	67.14 ± 14.96	DIC	7	92.85 ± 4.87	DIC	7	80.00 ± 9.57
CONTROL	7	7.85 ± 0.37	CONTROL	7	67.14 ± 7.55	CONTROL	7	91.42 ± 8.99	CONTROL	7	79.28 ± 7.31
		p			*p*			*p*			*p*
DEXT-MEL		0.006*	DEXT-MEL		0.546	DEXT-MEL		0.318	DEXT-MEL		0.884
DEXT-DIC		0.033*	DEXT-DIC		0.342	DEXT-DIC		0.038*	DEXT-DIC		0.11
DEXT-CONTROL		0.033*	DEXT-CONTROL		0.28	DEXT-CONTROL		0.073	DEXT-CONTROL		0.113
MEL-DIC		0.0001*	MEL-DIC		0.102	MEL-DIC		0.318	MEL-DIC		0.094
MEL-CONTROL		0.0001*	MEL-CONTROL		0.063	MEL-CONTROL		0.456	MEL-CONTROL		0.093
DIC-CONTROL		1.00	DIC-CONTROL		1.0	DIC-CONTROL		0.902	DIC-CONTROL		0.878

S.D., standard deviation; *N*, number of rats for each group; DEXT, dexketoprofen trometamol; MEL: meloxicam; DIC, diclofenac sodium.
* Significant at $p < 0.05$.

Table 4
The descriptive data of the mean values, standard deviations and *p* values related to kidney histopathology for each group.

Tubular necrosis/atrophy			Tubular vacuolar changes			Fibrosis			Vascular congestion/thrombosis			Interstitial inflammation		
Groups	*N*	Mean ± S.D.	Groups	*N*	Mean ± S.D.	Groups	*N*	Mean ± S.D.	Groups	*N*	Mean ± S.D.	Groups	*N*	Mean ± S.D.
DEXT	7	1.71 ± 0.75	DEXT	7	1.57 ± 0.78	DEXT	7	0.71 ± 0.75	DEXT	7	1.28 ± 0.95	DEXT	7	0 ± 0
MEL	7	1.42 ± 0.78	MEL	7	1.00 ± 0.81	MEL	7	0.14 ± 0.37	MEL	7	0.57 ± 0.78	MEL	7	0 ± 0
DIC	7	1.28 ± 0.48	DIC	7	1.00 ± 0.57	DIC	7	0.42 ± 0.53	DIC	7	0.42 ± 0.53	DIC	7	0.14 ± 0.37
CONTROL	7	0 ± 0	CONTROL	7	0 ± 0	CONTROL	7	0 ± 0	CONTROL	7	0 ± 0	CONTROL	7	0 ± 0
		p			*p*			*p*			*p*			*p*
DEXT-MEL		0.389	DEXT-MEL		0.24	DEXT-MEL		0.096	DEXT-MEL		0.133	DEXT-MEL		1
DEXT-DIC		0.244	DEXT-DIC		0.155	DEXT-DIC		0.475	DEXT-DIC		0.059	DEXT-DIC		0.317
DEXT-CONTROL		0.001*	DEXT-CONTROL		0.001*	DEXT-CONTROL		0.024*	DEXT-CONTROL		0.003*	DEXT-CONTROL		1
MEL-DIC		0.872	MEL-DIC		1	MEL-DIC		0.254	MEL-DIC		0.827	MEL-DIC		0.317
MEL-CONTROL		0.001*	MEL-CONTROL		0.009*	MEL-CONTROL		0.317	MEL-CONTROL		0.061	MEL-CONTROL		1
DIC-CONTROL		0.001*	DIC-CONTROL		0.002*	DIC-CONTROL		0.06	DIC-CONTROL		0.06	DIC-CONTROL		0.317

S.D., standard deviation; *N*, number of rats for each group; DEXT, dexketoprofen trometamol; MEL, meloxicam; DIC, diclofenac sodium.
* Significant at $p < 0.05$.

Table 5
The descriptive data of the mean values, standard deviations and *p* values related to liver histopathology for each group.

Hepatocyte degeneration			Bilier ductal proliferation			Cytoplasmic eosinophilia			Paranchymal necrosis			Central venous congestion/ thrombosis			Portal area inflammation			Sinosoidal dilation		
Groups	*N*	Mean ± S.D.	Groups	*N*	Mean ± S.D.	Groups	*N*	Mean ± S.D.	Groups	*N*	Mean ± S.D.	Groups	*N*	Mean ± S.D.	Groups	*N*	Mean ± S.D.	Groups	*N*	Mean ± S.D.
DEXT	7	0.85 ± 0.69	DEXT	7	0.14 ± 0.37	DEXT	7	0.85 ± 0.69	DEXT	7	0.85 ± 0.69	DEXT	7	0.28 ± 0.48	DEXT	7	0.28 ± 0.48	DEXT	7	1.57 ± 1.13
MEL	7	1.00 ± 0.57	MEL	7	0.42 ± 0.53	MEL	7	0.57 ± 0.53	MEL	7	0.85 ± 0.69	MEL	7	0.14 ± 0.37	MEL	7	0.42 ± 0.53	MEL	7	1.28 ± 0.48
DIC	7	1.00 ± 0	DIC	7	0.28 ± 0.48	DIC	7	0.57 ± 0.53	DIC	7	0.14 ± 0.37	DIC	7	0.42 ± 0.53	DIC	7	0.14 ± 0.37	DIC	7	1.00 ± 0.57
CONTROL	7	0 ± 0	CONTROL	7	0 ± 0	CONTROL	7	0 ± 0	CONTROL	7	0 ± 0	CONTROL	7	0 ± 0	CONTROL	7	0 ± 0	CONTROL	7	0 ± 0
		p			*p*			*p*			*p*			*p*			*p*			*p*
DEXT-MEL		0.653	DEXT-MEL		0.254	DEXT-MEL		0.424	DEXT-MEL		1	DEXT-MEL		0.53	DEXT-MEL		0.591	DEXT-MEL		0.669
DEXT-DIC		0.533	DEXT-DIC		0.53	DEXT-DIC		0.424	DEXT-DIC		0.035*	DEXT-DIC		0.591	DEXT-DIC		0.53	DEXT-DIC		0.32
DEXT-CONTROL		0.008*	DEXT-CONTROL		0.317	DEXT-CONTROL		0.008*	DEXT-CONTROL		0.008*	DEXT-CONTROL		0.141	DEXT-CONTROL		0.141	DEXT-CONTROL		0.003*
MEL-DIC		1	MEL-DIC		0.591	MEL-DIC		1	MEL-DIC		0.035*	MEL-DIC		0.254	MEL-DIC		0.254	MEL-DIC		0.334
MEL-CONTROL		0.002*	MEL-CONTROL		0.06	MEL-CONTROL		0.023*	MEL-CONTROL		0.008*	MEL-CONTROL		0.317	MEL-CONTROL		0.06	MEL-CONTROL		0.001*
DIC-CONTROL		0.0001*	DIC-CONTROL		0.141	DIC-CONTROL		0.023*	DIC-CONTROL		0.317	DIC-CONTROL		0.06	DIC-CONTROL		0.317	DIC-CONTROL		0.002*

S.D., standard deviation; *N*, number of rats for each group; DEXT, dexketoprofen trometamol; MEL, meloxicam; DIC, diclofenac sodium.
* Significant at $p < 0.05$.

Reviewer's note: Kidney and liver adverse effects are known class effects of NSAIDs and have been noted in the label. However, impaired bone fracture healing has not been discussed in Mobic label. There is extensive literature on the effects of NSAIDs as a class on wound healing and bone healing specifically (Marquez-Lara et al., 2016). Given the extensive clinical history of meloxicam, the clinical significance of these nonclinical changes is not clear.

2. (Pehlivan et al. 2010) Comparison of the effects of repeated dose treatments of lornoxicam and meloxicam on renal functions in rats.

Male Sprague-Dawley rats (N=10/group) were administered either 0.9% NaCl, 5.8 mg/kg meloxicam, 1.3 mg/kg lornoxicam by the intraperitoneal (IP) route for 14 consecutive days. On Day 14, rats were placed in metabolic cages and their urine was collected for 24 h. After anesthesia was administered, blood samples were taken, followed by nephrectomy. The study tested the hypothesis that preferential cyclooxygenase-2 inhibitors (e.g., meloxicam) have a higher renal safety profile when compared with the nonspecific cyclooxygenase inhibitors (e.g., lornoxicam).

Key findings:

- Meloxicam produced changes in the serum analysis and urine analyses indicative of renal changes. However, with the exception of intra-tubular blood cell casts and interstitial congestion seen in 1 male that exhibited hematuria, no histopathologic changes were noted in the kidneys of these rats.

Noteworthy results of serum and urine analyses are summarized in the following tables:

Serum Analyses Results		
Parameter	**Control**	**5.8 mg/kg/day**
BUN (mg/dL)	20.61	33.18*
Creatinine (mg/dL)	0.60	0.67*
Sodium (mmol/L)	137.10	139.80*
Potassium (mmol/L)	4.56	8.95*
Creatinine Clearance (mL/min)	0.55	0.07*
Urine Analyses Results		
Parameter	**Control**	**5.8 mg/kg/day**
Total Protein (g/dL)	0.12	0.90*
Creatinine (mg/dL)	102.39	40.70*
N-acetyl-β-D-glucosaminidase (U/L)	5.04	19.74*
Sodium (mmol/L)	70.60	60.20*
Potassium (mmol/L)	87.50	44.00*
Density (g/mL)	1015.30	1043.70*
Volume (mL)	4.63	1.66*

*p< 0.05

One meloxicam-treated rat with hematuria and histopathologic findings of interstitial congestion and intra-tubular red blood cell casts. No other histopathologic findings seen the kidneys of meloxicam-treated rats.

Reviewer's note: There were no significant adverse effects observed in this study.

3. (Burukoglu et al. 2016) Effects of nonsteroidal anti-inflammatory meloxicam on stomach, kidney, and liver of rats.

Burukoglu et al. assessed the toxicity of meloxicam in rats administered daily IP injections of 15 mg/kg/day meloxicam for 15 days. Histopathologic changes were noted in the liver (mononuclear cell infiltration and pseudo-lobular formation), kidneys (glomerular stasis-related hypertrophy and focal interstitial nephritis), and stomach (atrophy and metaplasia in the surface and glandular epithelia) of meloxicam-treated rats.

The Applicant claims that "although, the author attributes the histopathologic findings to hepatic and renal excretion of the drug, it should be noted that IP injection has a markedly high failure rate because there is no visual confirmation that the injection was correctly administered. An incorrect IP administration into the peritoneal cavity can result in injury to intestine, urinary bladder, cecum, and other tissues in the cavity (Gaines Das and North, 2007). Pathologic changes in the stomach and kidney are known toxicities of meloxicam. No hepatic changes were seen in the carcinogenicity studies conducted in mice and rats or in the chronic toxicity studies conducted in rats and minipigs; therefore, hepatic changes seen in this study may be secondary to the route of administration."

Reviewer's note: Kidney and liver adverse effects are known class effects of NSAIDs and has been noted in the label.

7 Genetic Toxicology

No new genetic toxicology studies were submitted or required with this NDA.

8 Carcinogenicity

No new carcinogenicity studies were submitted or required with this NDA.

9 Reproductive and Developmental Toxicology

No new reproductive and developmental toxicology studies were submitted with the NDA. The Applicant will rely upon the data in the referenced product labeling. In addition, nine articles were submitted to this NDA (based on review search on using meloxicam during pregnancy and lactation) that reported potentially relevant developmental findings and these were evaluated further by this reviewer (see below). In addition, a tabulated summary of these studies was provided by the Sponsor (see Appendix 1).

1. ***(Uzun et al., 2015) Evaluation of the reproductive toxicity of naproxen sodium and meloxicam in male rats.***

In this study male rats were dosed with 1 mg/kg meloxicam via oral gavage for 35 days (human equivalent dose of 9.7 mg/60 kg based on body surface area; 0.6x the human dose based on BSA). Sperm count and motility; COX-1, COX-2, PGE1, PGE2, PGF2a tissue levels in testes; FSH, LH, and testosterone plasma; and histopathology of testes was examined.

Key findings:

- The 35 days of treatment with 1 mg/kg/day meloxicam decreased testicular levels of COX-1, prostaglandin E1 (PGE1), PGE2, prostaglandin F2α (PGF2α), catalase (Cat), glutathione peroxidase (GPx), and glutathione (GSH).

- No meloxicam-related effects were noted on testicular levels of COX-2 or on plasma levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone.

- Reduced sperm count and sperm motility, and cellular degeneration, tubular atrophy, vacuolization, congestion, and an increase in connective tissue in the testes were noted for meloxicam-treated male rats.

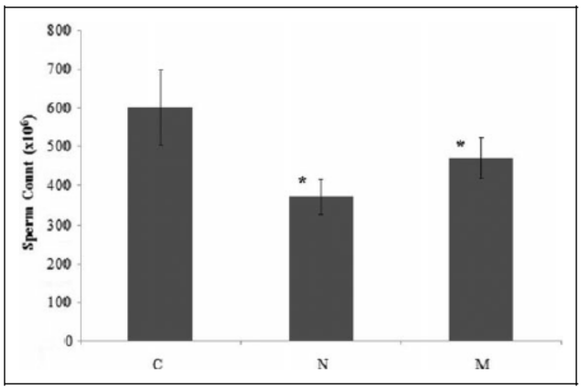


Figure 1. The effects of drug treatments after 35 days on sperm count in rats. C: distilled water-treated rats for 35 days, N: naproxen sodium-treated rats for 35 days, M: meloxicam-treated rats for 35 days. *$p < 0.05$: different from C.

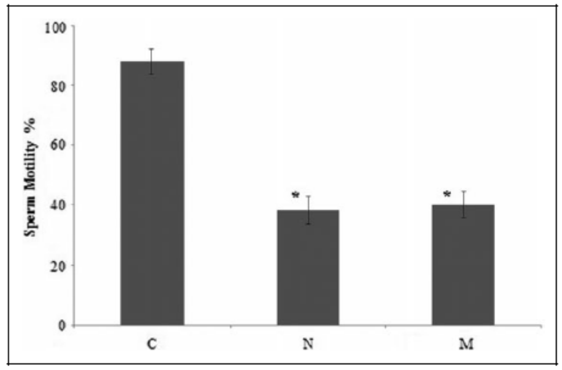


Figure 2. The effects of drug treatments after 35 days on sperm motility in rats. C: distilled water-treated rats for 35 days, N: naproxen sodium-treated rats for 35 days, M: meloxicam-treated rats for 35 days. *$p < 0.05$: different from C.

Table 2. The effects of drug treatments after 35 days on testis COX-1, COX-2, PGE_1, PGE_2, and $PGF_{2\alpha}$ levels in rats.

	C	N	M
COX-1 (pg/ml)	208.69 ± 26.11	171.95 ± 18.01[a]	189.56 ± 21.23[a]
COX-2 (ng/ml)	36.81 ± 5.16	33.48 ± 7.72	36.71 ± 8.42
PGE_1 (pg/ml)	73.01 ± 2.09	72.32 ± 1.06	69.83 ± 1.89[a,b]
PGE_2 (pg/ml)	136.67 ± 32.82	107.18 ± 18.61[a]	82.59 ± 23.31[a]
$PGF_{2\alpha}$ (pg/ml)	32.96 ± 6.14	24.32 ± 3.76[a]	25.76 ± 4.97[a]

C: control group; N: naproxen sodium group; M: meloxicam group; COX-1: cyclooxygenase-1; COX-2: cyclooxygenase-2; PGE_1: prostaglandin E_1; PGE_2: prostaglandin E_2; $PGF_{2\alpha}$: prostaglandin $F_{2\alpha}$.
[a]$p < 0.05$: different from C.
[b]$p < 0.05$: different from N.

Table 3. The effects of drug treatments after 35 days on testis GSH, GPx, SOD, and CAT levels in rats.

	C	N	M
GSH (μM)	55.67 ± 19.75	25.22 ± 5.69[a]	25.96 ± 6.51[a]
CAT (nmol/min/ml)	72.33 ± 12.52	58.02 ± 8.4[a]	53.70 ± 11.9[a]
SOD (U/ml)	3.22 ± 0.31	2.72 ± 0.37[a]	3.03 ± 0.28
GPx (nmol/min/ml)	75.32 ± 10.3	53.85 ± 17.24[a]	50.94 ± 9.72[a]

C: control group; N: naproxen sodium group; M: meloxicam group; GSH: glutathione; CAT: catalase; SOD: superoxide dismutase; GPx: glutathione peroxidase.
[a]$p < 0.05$: different from C.

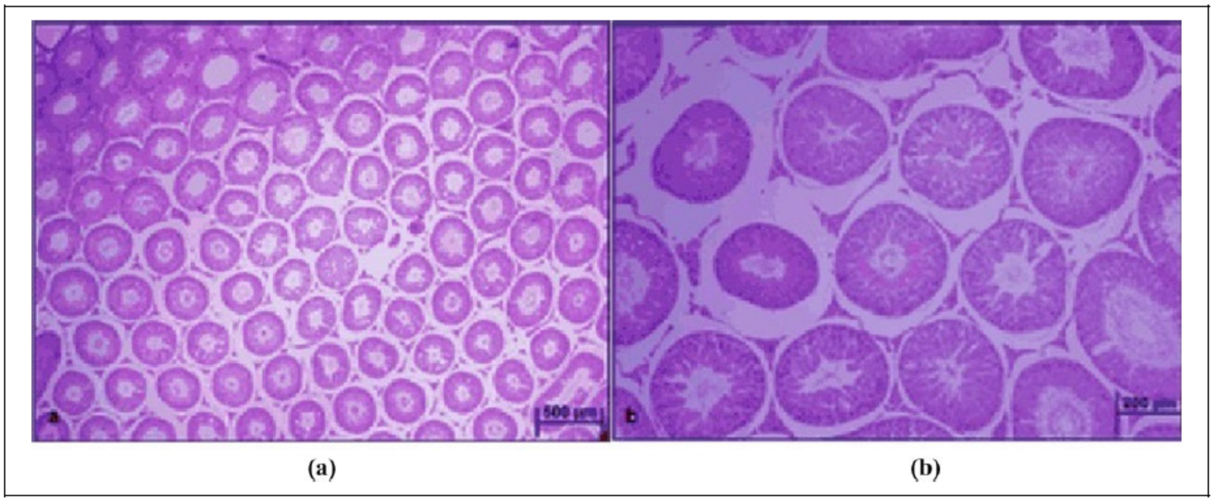


Figure 3. Assessment of testis light microscopy analysis in control male rats. The testes of rats from the control group revealed normal seminiferous tubules. (a) Hematoxylin and eosin stain, scale bar 500 μm and (b) hematoxylin and eosin stain, scale bar 200 μm.

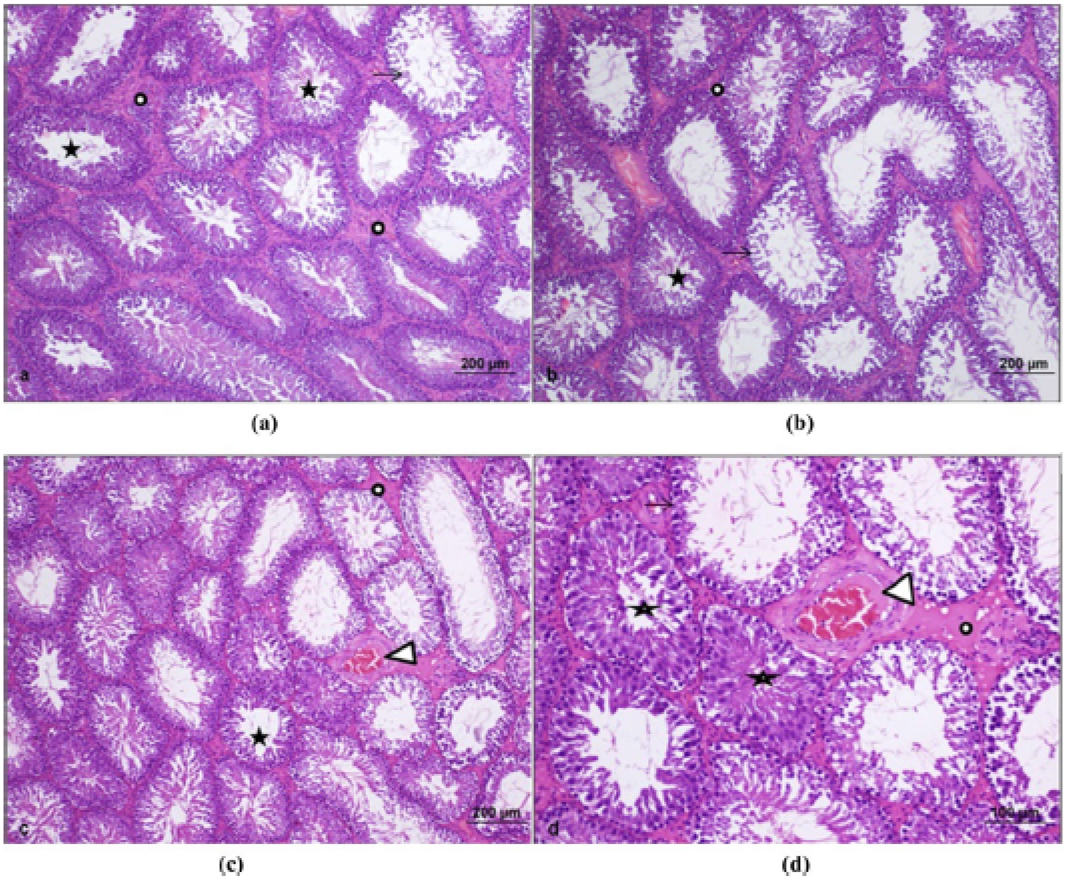


Figure 5. Assessment of testis light microscopy analysis in meloxicam-treated male rats. In the testis of rats treated with meloxicam, light microscopic examination revealed some seminiferous tubules containing near-normal spermatogenetic cells and ongoing spermatogenesis (*) as well as many damaged tubules (→), interstitial vascular congestion (▶), and increased concentration of connective tissue (○). (a) Hematoxylin and eosin stain, scale bar 200 µm; (b) hematoxylin and eosin stain, scale bar 200 µm; (c) hematoxylin and eosin stain, scale bar 200 µm; and (d) hematoxylin and eosin stain, scale bar 100 µm.

Reviewer's note: These results suggest that the mechanism of these effects may be a result of the inhibition of prostaglandin synthesis with a potential for oxidative stress providing a secondary influence. However, similar testicular changes are not described in the referenced Mobic labeling, which states that oral doses of up to 9 mg/kg in males did not impair male fertility (6x the MDD based on body surface area for TRADENAME Meloxicam ODT). However, it should be noted that male rats are far more fertile than humans; therefore, the changes reported by Uzun may not have resulted in a decrease fertility as measured in mating studies.

Similar testicular effects have been reported with ibuprofen, indomethacin, naproxen, acetaminophen, and aspirin suggesting a potential class effect (Mazaud-Guittot et al., 2013, Kristensen et al., 2016, Ben Maamar et al., 2017, Hay-Schmidt et al., 2017). Given the potential for class effects, the results of this study should be considered for inclusion in labeling. Potential language for 13.1 could read:

In a published study, oral administration of 1 mg/kg meloxicam (0.6x the maximum human daily dose for TRADENAME Meloxicam ODT) to male rats for 35 days resulted in decreased sperm count and motility and histopathological evidence of testicular degeneration.

A risk summary statement should also be included in Section 8.3.

2. (Salhab et al., 2001) Meloxicam inhibits rabbit ovulation

This paper assessed meloxicam-related effects on ovulation when administered as a single IP dose at 2, 5, or 8 hours post coitus (PC) or 14 hours post ovulation (24 hours PC) in rabbits. The doses assessed ranged from 2.5 mg/kg to 20 mg/kg.

Key findings:

- In this study, meloxicam inhibited ovulation both time- and dose-dependently with complete inhibition when 10 mg/kg was administered at 5 or 8 hours PC or 20 mg/kg was administered 2 or 5 hours. Lower doses of 5 and 2.5 mg/kg produced partial inhibition of pregnancy.

- When administered post-ovulation (24 hours PC), 4 of 5 females and 3 of 4 females administered 10 mg/kg and 20 mg/kg, respectively, were pregnant compared to 12 of 13 control.

- Histopathologic examination of the ovaries from animals given 20 mg/kg showed a dilatation of the Graafian follicles and some of the follicles that lost ova were cystically dilated with severe hemorrhage.

Table 1
The effects of meloxicam administered before ovulation on maternal body weight and pregnancy rate

Treatment (mg/kg)	Maternal body weight (g)			Number of pregnant rabbits/Number of treated rabbits	Pregnancy (%)
	Initial	Final	Gain (%)		
Control	2297 ± 333	2480 ± 352	7.97	12/13	92.3
Indomethacin					
20	2020 ± 170	2250 ± 165	11.3	0/3	0.0
Meloxicam					
20	2403 ± 323	2479 ± 373	3.15	0/16	0.0
10	2484 ± 334	2509 ± 328	1.0	1/12	8.3
5	2316 ± 316	2578 ± 303	11.1	2/10	20
2.5	2388 ± 252	2548 ± 103	6.7	3/5	60

Table 2
The effects of meloxicam on pregnancy rate administered at different times

Meloxicam dose (mg/kg)	Time of treatment (h postcoitus)	Number of pregnant rabbits/Number of treated rabbits	Pregnancy (%)
20	2	0/11	0.0
	5	0/5	0.0
	24	3/4	75.0
10	2	1/4	25.0
	5	0/4	0.0
	8	0/4	0.0
	24	4/5	80.0
5	5	1/6	16.7
	8	3/4	75.0
2.5	5	3/5	60.0

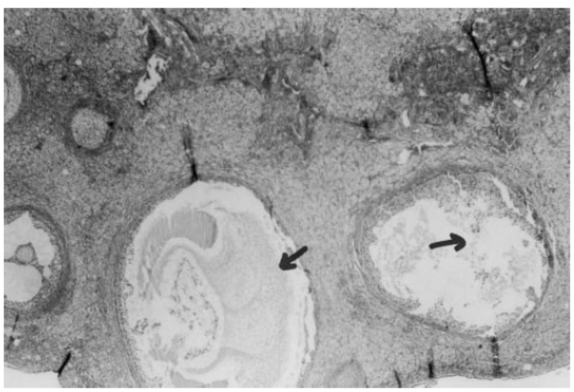


Fig. 1. Severely dilated and hemorrhagic graffian follicles (arrow) from meloxicam 20 mg/kg-treated rabbit (Hematoxylin and eosin, 200×).

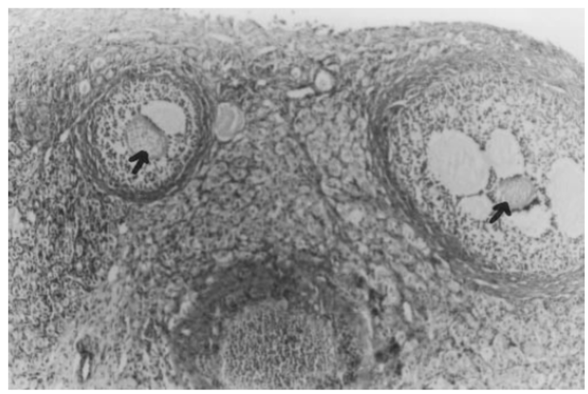


Fig. 2. Mature graffian follicles containing ova (arrow) from control rabbit (H and E, 200×).

Reviewer's note: these data shows that the contraceptive effect is due to dose- and time-dependent inhibition of ovulation. There is another publication, which is discussed below, by the same group that further assessed meloxicam-related effects on ovulation in the rabbits. See Reviewer's notes for this reviewer's combined assessment.

3. ***(Salhab et al., 2003) Further investigation on meloxicam contraceptivity in female rabbits: luteinizing unruptured follicles, a microscopic evidence.***

Bred females were dosed at 5 hours PC with 20 mg/kg meloxicam (oral) or 14.9 g/kg (intravaginal). None of the females that received the full dose were pregnant at the GD10 C-section. Microscopic examination of the ovaries showed an irregular surface resulting from different sized cysts and some of the cystic follicles contained retained ova. Immunohistochemical assessment for estrogen and progesterone showed positive staining in the granulosa cells and unruptured follicles.

Reviewer's note: Together, these data from two publications support the conclusion that the contraceptive effect is due to the failure of follicular rupturing.

These findings are currently reflected in the MOBIC and other NSAIDs labels in Section 8.3 Females and Males of Reproductive Potential. The Mobic label reflects the current class labeling for NSAIDs as follows. Similar language is appropriate for this drug product.

> "Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including MOBIC, 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 have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including MOBIC, in women who have difficulties conceiving or who are undergoing investigation of infertility."

4. (McCann et al., 2013) The COX-2 inhibitor meloxicam inhibits pregnancy when administered as an emergency contraceptive to nonhuman primates.

Meloxicam was administered orally (0.5 mg/kg/day) to proven fertile female cynomolgus macaques using one emergency contraceptive model and three monthly contraceptive models. In the emergency contraceptive model, females were bred with a proven fertile male once 2±1 days before ovulation, returned to the females' home cage, and then received 5 days of meloxicam treatment. In the monthly contraceptive models, females were cocaged for breeding with a proven fertile male for a total of 5 days beginning 2±1 days before ovulation. Animals received meloxicam treatment (1) cycle days 5–22, or (2) every day, or (3) each day of the 5-day breeding period. Female were then assessed for pregnancy.

Key findings:

- The pregnancy rate with meloxicam administration using the emergency contraception model was 6.5%, significantly lower than the pregnancy rate of 33.3% when vehicle without meloxicam was administered.
- Pregnancy rates with the three monthly contraceptive models (75%–100%) were not consistent with preventing pregnancy.

Conclusion: This study further supports NSAID class labeling language regarding effects of NSAID on fertility through interference with ovulation. This is currently reflected in Section 8.3, as noted above.

5. (Hester et al., 2010) Oral administration of the cyclooxygenase-2 (COX-2) inhibitor meloxicam blocks ovulation in non-human primates when administered to simulate emergency contraception

Four sequential menstrual cycles were studied. In Cycle 1, a serum sample was obtained each day and assayed for estradiol, progesterone and luteinizing hormone; first menses was also noted to establish parameters of a normal menstrual cycle for each animal. In Cycle 2, meloxicam was administered orally once each day for 5 days beginning at either mid-follicular, late-follicular or periovulatory phase of the menstrual cycle. Daily serum samples and menses were assessed as for Cycle 1. In Cycle 3, the follicle-bearing ovary was removed 2 days after the expected day of ovulation. In Cycle 4, monkeys received the 5-day courses of oral meloxicam as in Cycle 2, and the remaining ovary was removed. Ovaries were examined for the presence of an oocyte within the follicle.

Key finding:

- Meloxicam treatment in Cycle 2 did not alter hormone levels or the luteal phase length.
- Follicles of ovaries removed during Cycle 3 did not contain oocytes, indicating successful ovulation.
- Follicles did contain oocytes after meloxicam treatment beginning in the mid-follicular (67%), late-follicular (100%) or periovulatory (50%) phase of Cycle 4, indicating failure of ovulation.

Conclusions: A 5-day course of oral meloxicam administered around the time of ovulation reduced the rate of oocyte release without alteration of reproductive hormones or menstrual cycle length.

Reviewer's note: These findings are currently reflected in the MOBIC and other NSAIDs labels in Section 8.3 Females and Males of Reproductive Potential. The Mobic label reflects the current class labeling for NSAIDs as follows. Similar language is appropriate for this drug product.

> "Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including MOBIC, 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 have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including MOBIC, in women who have difficulties conceiving or who are undergoing investigation of infertility."

6. ***(Cappon et al., 2003) Relationship between cyclooxygenase 1 and 2 selective inhibitors and fetal development when administered to rats and rabbits during the sensitive periods for heart development and midline closure***

This study assessed the effects COX-1 and COX-2 inhibition on fetal heart development and midline closure in rats and rabbits by administering meloxicam to pregnant females during the sensitive period of development in each species (rats, 15 mg/kg/day on GD 9 and 10 and rabbits, 600 mg/kg on GD 9, 10, and 11).

Key findings:

- Meloxicam-related maternal toxicity occurred in rats (decreased body weights on GD 9 to GD 12) and rabbits (loose/liquid stool in rabbits).

- With the exception of a decrease in fetal body weight (9% lower than control), high doses of meloxicam did not produce any fetal developmental effects. Specifically, no midline defects, diaphragmatic hernia, or ventricular septal defects were noted.

Table 4

Rat Fetal Evaluations From Dams Treated With Non-steroidal Anti-Inflammatory Drugs on Gestational Days 9 and 10

	Dose group[a]						
	Control 262 (20)	CJ-19,209 192 (15)	Meloxicam 217 (16)	Diclofenac 177 (14)	Diflunisal 185 (14)	Ibuprofen 252 (19)	Ketorolac 247 (19)
External findings							
Polydactyly	—	—	—	2(1)[b]	—	—	—
Syndactyly	—	—	—	1(1)[b]	—	—	—
Hindlimb hypoflexion	—	—	—	1(1)[c]	—	—	—
Acaudate	—	—	—	1(1)[c]	—	—	—
Anus imperforate	—	—	—	1(1)[c]	—	—	—
Visceral findings							
Heart							
VSD, membranous	1(1)	1(1)	—	1(1)	8(7)	12(8)	3(3)
Blood vessels							
Subclavian retroesophageal	—	—	—	—	—	1(1)	—
Eyes							
Microphthalmia	—	—	—	—	—	1(1)	—
Kidneys							
Renal papilla absent	—	—	—	—	—	1(1)	—

[a]Fetuses (litters)
[b,c]Multiple findings for one fetus.
VSD, ventricular septal defect.

Table 8
Rabbit Fetal Evaluations from Does Treated with Nonsteroidal Anti-Inflammatory Drugs on Gestational Days 9, 10, and 11

	Dose group[a]						
	Control 147 (18)	CJ-19,209 157 (20)	Meloxicam 132 (16)	Diclofenac 124 (16)	Diflunisal 109 (14)	Ibuprofen 158 (19)	Ketorolac 156 (18)
External findings							
Petechia	—	—	—	—	—	—	1(1)
Gastroschisis	—	—	—	—	—	1(1)	—
Forepaw hyperflexion	1(1)	—	—	—	—	—	—
Omphalocele	—	—	—	—	1(1)	—	—
Visceral findings							
Heart							
VSD, membranous	—	—	—	—	2(2)[d]	1(1)	—
VSD, muscular					1(1)[b]		
Blood vessels							
Enlarged aortic arch	—	—	—	—	1(1)[b]	—	—
Subclavian retroesophageal	—	—	—	—	1(1)	—	—
Absent innominate artery	—	—	—	—	1(1)	—	—
Accessory vessels	—	—	—	—	6(4)	—	1(1)
Brain							
Lateral ventricles dilated	1(1)	—	—	—	—	—	2(2)
Diaphragm							
Diaphragmatic hernia	—	—	—	—	1(1)	—	—
Eyes							
Microphthalmia	—	—	—	—	6(4)[c,d,e]	—	—
Hemorrhage	—	—	—	—	2(2)[c,e]	—	—
Hemorrhagic ring	—	1(1)	—	—	—	—	—

[a]Fetuses (litters).
[b–e]Multiple findings for one fetus.
VSD, ventricular septal defect.

Reviewer's note: These doses of 15 mg/kg/day in rats and 600 mg/kg/day in rabbits provided safety margins of up to 9.7 and 778 times greater, respectively, the MRHD based on BSA comparison for TRADENAME Meloxicam ODT. [redacted] (b) (4)

The Mobic label states "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 (78-fold greater than the MRHD based on BSA comparison). The no effect level was 20 mg/kg/day (26-fold greater than the MRHD based on BSA conversion)."

The published study showed that a 10-fold higher dose of meloxicam (600 mg/kg) did not produce heart defects when given during GD 9-11, which they argue is the most sensitive period for fetal heart development, versus effects observed at 60 mg/kg when given throughout the period of organogenesis. The lack of heart findings with higher doses than tested in the Mobic label during the sensitive period of heart development are contradictory to the findings described in the Mobic label. [redacted] (b) (4)

(b) (4)

7. (Thaete et al., 2013) Impact of anaesthetics and analgesics on fetal growth in the mouse.

This study was designed to test the effects of specific anesthetic and analgesic agents, including meloxicam, on fetal development when dosed at times approximating fertilization (E0), attachment (E4), beginning of organogenesis (E6), end of organogenesis (E12), and the logarithmic growth phase (E15). At term (E18), fetal and placental growth were evaluated, morphological analyses were performed, and skeletal measurements were conducted.

<u>Key findings:</u>

- A slight, but statistically significant decrease in fetal weight and in the length of the humerus were noted when meloxicam (2 mg/kg) was administered to pregnant mice by IM injection one on GD 0 or on both GD 0 and 1 (during fertilization) for two days. The data showed that fetal weights and humerus lengths were significantly correlated for meloxicam (P<0.01).

Table 1. Anaesthetic and analgesic recommendations for mouse pregnancy.

	Gestation day and phase				
	E0	E4	E6	E12	E15
	Fertilization	Attachment	Begin organogenesis	End organogenesis	Growth phase
Anaesthetics					
Ketamine/xylazine	✗	✗	✓	✗	✗
Isoflurane	✗	✓	✗	✓	✓
Tribromoethanol	✓	✓	✗	✗	✓
Analgesics					
Buprenorphine	✓	✗	✗	✓	✓
Meloxicam	✗	✓	✓	✓	✓

✓: acceptable; ✗: not recommended

<u>Reviewer's note</u>: The dose tested (2 mg/kg/day in mice) provides an exposure margin of only 0.6 times the MRHD of 15 mg of TRADENAME Meloxicam ODT based on BSA comparison. These findings are not completely unexpected since the reference product label notes that meloxicam caused embryofetal death in rats and rabbits when administered during the period of organogenesis at doses equivalent to 0.65 – and 6.5 times, respectively, the MRHD of 15 mg of Mobic. As the embryolethality findings described in the reference product labeling are more severe, the reviewer does not feel

it necessary to describe the growth effects in the TRADENAME Meloxicam ODT labeling.

8. *(Jaffal et al., 2006) Effects of meloxicam on implantation and parturition of rat.*

To evaluate the effect of meloxicam on implantation, rats were dosed orally with 7.5 and 10 mg/kg/day from Day 1 through 3 or from Day 3 through 5 of gestation, respectively. While for the parturition effect, rats were dosed orally by the above doses from Day 20 through 22 of gestation.

Key findings:

- The number of implantation sites was significantly decreased in all treated groups in a dose- and time-dependent manner. Whereas the number of resorption sites was significantly increased in all meloxicam treated groups.
- Meloxicam significantly prolonged the duration time of delivery in a dose-dependent manner.
- Significantly less viable fetuses and pups were delivered per female treated with meloxicam.

Table 1: Effect of meloxicam treatment on rat implantation.

Parameters	*Early implantation (1-3 days)*			*Late implantation (3-5 days)*		
	Vehicle	*7.5mg/kg*	*10mg/kg*	*Vehicle*	*7.5mg/kg*	*10mg/kg*
Number of pregnant rats	9	8	8	8	9	8
Viable implanted sites (M ± SD)	9.78 ± 1.99	7.4 ± 5.0	0.13 ± 0.35*	7.63 ± 0.5	5.89 ± 6.11	0.0 (all dead)
Adsorption sites (M ± SD)	0.56 ± 1.67	5.4 ± 5.6*	7.6 ± 2.1*	0.5 ± 1.4	6.56 ± 5.7*	8.0 ± 1.85*
Number of pregnant rats with viable implantation sites	9	6.5	1	7	5	0.0 (all dead)
(%):	100	75.0	12.5	87.5	55.6	0.0 (all dead)

** P < 0.05 as compared to vehicle values.*

Figure 1: Normal uterus with intact ovaries of control rats. Rats were sacrificed on day 10 of gestation. Ten normal fetuses appear with no absorbing sites. Bar represents 10 mm.

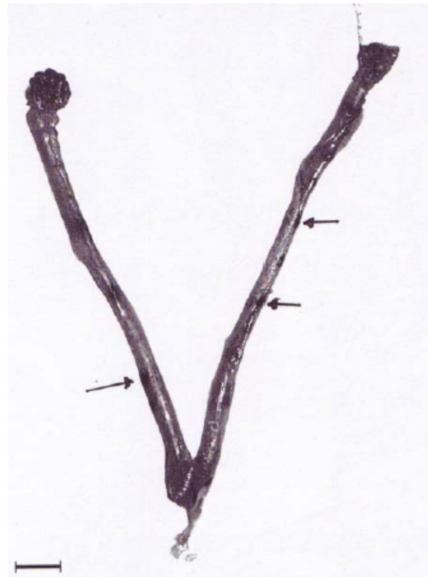


Figure 2: The uterus of meloxicam-treated rats (10 mg/kg) on days 3,4 and 5 of gestation (Late implantation). Notice the resorping sits (arrows) and the absence of fetuses. Bar represents 10 mm.

Table 2: Effect of meloxicam treatment on rat late pregnancy outcome.

	Treatment		
Parameter	**Vehicle**	**7.5 (mg / kg)**	**10.0 (mg / kg)**
Number of pregnant rats	10	8	8
Viable fetuses (M ± SD)	8.18 ± 1.6	6.37 ± 3.85*	6.38 ± 4.1*
(%)	(93.7)	(79.9)	(79.9)
Fetus body weight (g)	5.62 ± 1.0	5.53 ± 0.57	4.76 ± 0.82
Dead fetuses (M ± SD)	0.55 ± 0.82	1.6 ± 3.03*	2.75 ± 4.53*
Maternal plasma oxytocin (ng/ml)	104 ± 83	116 ± 67	739 ± 311*

*** P < 0.05 as compared to vehicle values.**

Table 3: Effect of meloxicam on rat parturition.

	Treatment		
Parameter	**Vehicle**	**7.5 (mg / kg)**	**10.0 (mg / kg)**
Number of pregnant delivered rats	11	11	11
Viable pups (M ± SD)	6.2 ± 2.64	2.0 ± 2.9*	0.57 ± 1.51*
(%)	(80)	(25.9)	(7.0)
Pup body weight (g)	5.5 ± 0.76	5.3 ± 0.67	5.6 ± 0.42
Dead pups (M ± SD)	1.5 ± 2.5	5.73 ± 3.43*	7.56 ± 1.24*
Parturition day (PD) (%)			
22:	1 (9.1)	1 (9.1)	0.0
23:	9 (81.2)	1 (9.1)	0.0
24:	1 (9.1)	2 (18.2)	2.0 (18.2)
25:	0.0	5 (45.5)	5.0 (45.5)
26:	0.0	2 (18.2)	4.0 (36.4)
Parturition day (M ± SD):	23.0 ± 0.63	24.55 ± 1.2*	25.14 ± 1*

*** P < 0.05 as compared to vehicle values.**

Reviewer's note: These findings are currently reflected in the Mobic and other NSAIDs labels. Class labeling for NSAIDs currently state "In animal studies, administration of prostaglandin synthesis inhibitors, such as meloxicam, resulted in increased pre- and post-implantation loss" and "In animal studies, NSAIDs, including meloxicam, inhibit prostaglandin synthesis, cause delayed parturition, and increase the incidence of stillbirth." in Section 8.1 Risk Summary.

9. ***(Paksoy and Kirbas, 2017) Evaluation of the contraceptive effects of carprofen, flunixin meglumine, and meloxicam in rats.***

The objective of this study was to determine the suitability of meloxicam for use in emergency contraception. A single dose of 2 mg/kg meloxicam was administered to rats on Gestation Day (GD) 3 (third day of mating). The control group received saline. The rats were sacrificed on GD 7. Luteal spots and implantation sites were recorded. Pre-implantation loss was calculated by subtracting the number of luteal spots from the number of implantation sites.

Key findings: The mean number of luteal spots was similar between the control and meloxicam-treated dams; however, the mean number of implantation sites was decreased and only 37.5% of the females were pregnant compared to 100% of the control females.

Reviewer's comments: These findings are currently reflected in the Mobic and other NSAIDs labels. Class labeling for NSAIDs currently state "In animal studies, administration of prostaglandin synthesis inhibitors, such as meloxicam, resulted in increased pre- and post-implantation loss" in Section 8.1 Risk summary.

10 Special Toxicology Studies

No new carcinogenicity studies were submitted with this NDA.

11 Integrated Summary and Safety Evaluation

See Executive Summary

12 Appendix/Attachments

Tabulated Summary of Published Nonclinical Toxicity Literature

Species/Strain	Method of Admin./Vehicle	Duration of Dosing	Daily Dose[a] (mg/kg)	Number/ Sex per Group	Noteworthy Findings (Meloxicam-Related only)
In Vivo, Repeat-Dose Toxicity					
Title: *Comparison of the effects of dexketoprofen trometamol, meloxicam and diclofenac sodium on fibular fracture healing, kidney and liver: an experimental rat model. Inal et al. 2014.* ***Parameters Evaluated:*** *light microscopy of kidneys and liver.*					
Rat/Sprague-Dawley	IM/Not specified	10 days	0 and 0.2	7/Male	Results: mild renal tubular necrosis and vacuolization and mild hepatic parenchymal necrosis. No histopathologic changes were seen in the Control tissues.
Title: *Comparison of the effects of repeated dose treatments of lornoxicam and meloxicam on renal functions in rats. Pehlivan et al. 2010.* ***Parameters Evaluated:*** *clinical chemistry, urine analysis, light microscopy of kidneys.*					
Rat/Sprague-Dawley	IP/Saline	14 days	0 and 5.8	10/Male	Noteworthy results of serum and urine analyses are summarized in the following tables: (see tables below) *p< 0.05 One meloxicam-treated rat with hematuria and histopathologic findings of interstitial congestion and intra-tubular red blood cell casts. No other histopathologic findings seen the kidneys of meloxicam-treated rats.

Serum Analyses Results		
Parameter	**Control**	**5.8 mg/kg/day**
BUN (mg/dL)	20.61	33.18*
Creatinine (mg/dL)	0.60	0.67*
Sodium (mmol/L)	137.10	139.80*
Potassium (mmol/L)	4.56	8.95*
Creatinine Clearance (mL/min)	0.55	0.07*
Urine Analyses Results		
Parameter	**Control**	**5.8 mg/kg/day**
Total Protein (g/dL)	0.12	0.90*
Creatinine (mg/dL)	102.39	40.70*
N-acetyl-β-D-glucosaminidase (U/L)	5.04	19.74*
Sodium (mmol/L)	70.60	60.20*
Potassium (mmol/L)	87.50	44.00*
Density (g/mL)	1015.30	1043.70*
Volume (mL)	4.63	1.66*

*p< 0.05

Species/Strain	Method of Admin./Vehicle	Duration of Dosing	Daily Dose[a] (mg/kg)	Number/ Sex per Group	Noteworthy Findings (Meloxicam-Related only)
Title: *Effects of nonsteroidal anti-inflammatory meloxicam on stomach, kidney, and liver of rats. Burukoglu et al. 2016.* ***Parameters Evaluated:*** *Light microscopy of liver, stomach, and kidneys.*					
Rat/Sprague-Dawley	IP/Saline	15 days	0 and 15	10/sex not specified	Parameters evaluated: light microscopy of liver, stomach, kidney. Results: Histopathology changes: liver: mononuclear cell infiltration and pseudo-lobular formation; kidney: glomerular stasis-related hypertrophy and focal interstitial nephritis; and stomach: atrophy and metaplasia in the surface and glandular epithelia. Conclusions: Meloxicam might cause hepatotoxicity, nephrotoxicity, and gastric metaplasia in rats at a used dose and duration. In addition, author states that the histopathologic findings were due to the excretion of the drug (50% from liver and 50% from kidneys). Note: Drug administration via IP injection has a notably high failure rate because there is no visual confirmation that the injection was correctly administered. Incorrect IP administration into the peritoneal cavity can result to injury to intestine, urinary bladder, cecum, and other tissues in the cavity. (Gaines Das et al. 2007)

Species/Strain	Method of Admin./Vehicle	Duration of Dosing	Daily Dose[a] (mg/kg)	Number/ Sex per Group	Noteworthy Findings (Meloxicam-Related only)
In Vivo, Male Reproductive Toxicity					
Title: *Evaluation of the reproductive toxicity of naproxen sodium and meloxicam in male rats. Uzun et al. 2015.* ***Parameters Evaluated:*** *COX-1, COX-2, PGE_1, PGE_2, $PGE_{2\alpha}$, GSH, GPx, CAT, SOD, FSH, LH, testosterone, sperm count, sperm motility, and microscopic examination of male reproductive tissues.*					
Rat/Wistar	Oral/Distilled water	35 days	0 and 1	10/Male	Results: Noteworthy data are summarized in the following tables.

Dose	Serum Hormone Levels: FSH (ng/mL)	LH (mU/mL)	Testosterone (ng/mL)	Testicular Levels of: COX-1 (ng/mL)	COX-2 (ng/mL)	GSH (µM)
0	61.9	12.0	2.20	209	36.8	55.7
1	64.9	10.9	2.58	190*	36.7	26.0*

Dose	Testicular Levels of: PGE_1 (pg/mL)	PGE_2 (pg/mL)	$PGF_{2\alpha}$ (pg/mL)	SOD (U/mL)	CAT (nmol/min/mL)	GPx (nmol/min/mL)
0	73.0	137	33.0	3.22	72.3	75.3
1	69.8*	82.6*	25.8*	3.03	53.7*	50.9*

Sperm Parameters

Dose	Sperm Count	Sperm Motility (%)
0	-	-
1	↓**	↓**

Histopathology, Testes (N = 10)

Dose	Number of Males with: Cellular degeneration	Tubular atrophy	Vacuolization	Congestion	Increase in connective tissue
	0	1	0	1	0
	9	5	5	10	10

* $P < 0.05$: different from control; ** $P < 0.001$

Conclusions: Meloxicam decreased the sperm count and motility and also induced the damage of seminiferous tubules as a direct effect without affecting plasma hormone levels. The changes may be a result of the inhibition of prostaglandin synthesis; however, the induction of oxidative stress may also be a secondary factor.

Species/Strain	Method of Admin./Vehicle	Duration of Dosing	Daily Dose[a] (mg/kg)	Number/ Sex per Group	Noteworthy Findings (Meloxicam-Related only)
In Vivo, Female Reproductive Toxicity					
Title: *Effects of meloxicam on implantation and parturition of rat. Jaffal et al. 2006* ***Parameters Evaluated:*** *Uterine contents, parturition, delivery data, gestation length.*					
Rat/Albino	Oral/0.15 M NaOH	3 days/ GD 0, 1, and 2; GD 2, 3 and 4; or GD 19, 20, and 21	0, 7.5, and 10	Varied/ Bred females	Results: Noteworthy data are summarized in the following tables.

Gestation Day 9; Uterine Results; Effects on Implantation

Daily Dose (mg/kg)	Mean Number Implantation Sites	Mean Number Resorption Sites	Percent with Viable Implantation Sites
Treatment: GD 0, 1, and 2			
0	9.78	0.56	100
7.5	7.4	5.4*	75
10	0.13	7.6*	12.5
Treatment: GD 2, 3, and 4			
0	7.63	0.5	87.5
7.5	5.89	6.56*	55.6
10	0	8.0*	0

Gestation Day Uterine Results; Effects on Late Pregnancy (GD 22 C-Section)

Daily Dose (mg/kg)	Mean Number of Viable Fetuses	Mean Number Dead Fetuses	Plasma Oxytocin (ng/mL)
Treatment: GD 19, 20, and 21			
0	8.18	0.55	104
7.5	6.37*	1.6*	116
10	6.38*	2.75*	739*

Gestation Day Uterine Results; Effects on Late Pregnancy/Parturition

Daily Dose (mg/kg)	Mean Number of Viable Pups	Mean Number Dead Pups	Mean Gestation Length
Treatment: GD 19, 20, and 21			
0	6.2	1.5	23.0
7.5	2.0*	5.73*	24.55*
10	0.57*	7.56*	25.14*

*$P < 0.05$

In this study, meloxicam inhibited implantation and parturition in a time- and dose-related manner.

Species/Strain	Method of Admin./Vehicle	Duration of Dosing	Daily Dose[a] (mg/kg)	Number/ Sex per Group	Noteworthy Findings (Meloxicam-Related only)
Title: *Evaluation of the contraceptive effects of carprofen, flunixin meglumine and meloxicam in rats. Paksoy and Kirbas 2017.* ***Parameters Evaluated****: Uterine contents, corporal lutea, and pregnancy.*					
Rat/Sprague-Dawley	SC/Vehicle not specified	Single dose on GD 3	0 and 2	8/Bred females	Results: the noteworthy data are summarized in the following tables.

Gestation Day 7; Uterine Results; Effects on Implantation

Daily Dose (mg/kg)	Mean Number Implantation Sites	Mean Number Luteal Spots	Percent Pregnant
Treatment: GD 3			
0	11.38	11.38	100
2	3.00	12.63	37.5

Species/Strain	Method of Admin./Vehicle	Duration of Dosing	Daily Dose[a] (mg/kg)	Number/ Sex per Group	Noteworthy Findings (Meloxicam-Related only)
Title: *Meloxicam inhibits rabbit ovulation. Salhab et al. 2001.* ***Parameters Evaluated****: Fertility, uterine contents, corpora lutea, ovarian histopathology.*					
Rabbit/ Californian	IP/0.15 M NaOH	Single dose/2, 5, or 8 hours post-coitus (PC) or 14 hours post-ovulation (24-hr PC)	0 (time not specified) 2.5, 5, 10, and 20 (2, 5, and 8 hours PC) 10 and 20 (14 hours post-ovulation	Varied/ Bred females (see tabulated data)	Results: Noteworthy data are summarized in the following tables.

Pregnancy Results; Meloxicam-Treated Does

Dose (mg/kg)	Time of Treatment (hr PC)	Number Bred	Number Pregnant	Percent Pregnant
0	NA	13	12	92.3
2.5	5	5	3	60.0
5	5	6	1	16.7
	8	4	3	75.0
10	2	4	1	25.0
	5	4	0	0.0
	8	4	0	0.0
	24	5	4	80.0
20	2	11	0	0.0
	5	5	0	0.0
	24	4	3	75.0

Gestation Day 10 Uterine Results; Meloxicam-Treated Does

Dose (mg/kg)	Mean Number Implantation Sites	Mean Number Corpora Lutea	Plasma Progesterone (ng/mL)
0	5.85	6.31	11.1
Pre-ovulation (2, 5, or 8 Hours PC)			
2.5	2.4	6.0	11.2
5	< 1	4.33	6.37
10	< 1	5.17	9.16
20	0	4.73	6.78
Post-ovulation (24 Hours PC)			
10	5.6	5.0	7.86
20	6.75	6.75	9.03

Histopathology: dilatation of Graafian follicles. Some were cystically dilated with severe hemorrhage in the follicles that lost ova.

Conclusions: administration of meloxicam to sperm-positive rabbits resulted in significant dose- and time-dependent inhibition of ovulation.

Species/Strain	Method of Admin./Vehicle	Duration of Dosing	Daily Dose[a] (mg/kg)	Number/ Sex per Group	Noteworthy Findings (Meloxicam-Related only)
Title: *Further investigation on meloxicam contraceptivity in female rabbits: luteinizing unruptured follicles, a microscopic evidence.* *Salhab et al 2003.* ***Parameters Evaluated:*** *Fertility, uterine contents, corpora lutea, ovarian histopathology, immunohistochemistry.*					
Rabbit/ Californian	Oral/0.15 M NaOH Intra-vaginal/ Witespol® bases	Single dose/5 hours PC	Oral: 0, 20 Intravaginal: 0, 14.9	Varied/ Bred females (see tabulated data)	Results: Noteworthy data are summarized in the following tables.

Pregnancy Results

Dose (mg/kg)	Time of Treatment (hr PC)	Number Bred	Number Pregnant	Percent Pregnant
Oral Gavage Dosing				
0	5	6	6	100
20	5	6	0	0
Intravaginal Dosing				
0	5	5	5	100
14.9	5	8*	3*	37.5*

Gestation Day 10 Uterine Results

Dose	Mean Number Implantation Sites	Mean Number Corpora Lutea	Plasma Progesterone (ng/mL)
Oral Gavage Dosing			
0	6.33	7.0	18.3
20	0	7.67	27.4
Intravaginal Dosing			
0	6.4	7.6	23.2
14.9	2.13*	7.8	25.0

*As noted in the text, 3 of 8 does consistently refused vaginal insertion of the suppository. None of the 5 does that accepted the suppository was pregnant.

Histopathology: the surface of ovaries appeared irregular and dilated because of the presence of different sized cysts. Some cystic follicles with retained ova. Immunohistochemical staining for estrogen and progesterone showed positive staining in the granulosa cells and unruptured follicles.

Conclusions: Administration of meloxicam by oral or intravaginal routes resulted in inhibition of ovulation. Histopathologic and immunohistochemical data suggest this effect is due to the entrapment of the oocyte by prevention of the follicular rupturing.

Species/Strain	Method of Admin./Vehicle	Duration of Dosing	Daily Dose[a] (mg/kg)	Number/ Sex per Group	Noteworthy Findings (Meloxicam-Related only)
Title: *Oral administration of the cyclooxygenase-2 (COX-2) inhibitor meloxicam blocks ovulation in non-human primates when administered to simulate emergency contraception.* *Hester et al. 2010* ***Parameters Evaluated:*** *Hormone levels, pregnancy, oocyte release.*					
Monkey/ Cynomolgus	Oral/Food Treats	5 days Mid-follicular Late-follicular Peri-ovulatory	0 and 0.5. Pairwise treatment design; each monkey received vehicle and meloxicam .	4/Adult females per treatment phase	Results: Noteworthy data are summarized in the following tables.

Menstrual Cycle Parameters

Treatment Phase	Peak LH (ng/mL)		Length of Luteal Phase (days)	
	Control	Meloxicam	Control	Meloxicam
Mid-follicular	29.5	23.2	16.3	15.0
Late-follicular	18.0	11.9	14.5	16.3
Peri-ovulatory	10.4	16.1	17.8	15.8

Number and location of Oocytes in the Ovaries

Treatment Phase	Females with Oocytes Present in Ovaries		Location of Oocytes
	Control	Meloxicam	Meloxicam
Mid-follicular	0/3	2/3	In antrum
Late-follicular	0/4	4/4	Near follicle basement membrane
Peri-ovulatory	0/4	2/4	Near follicle basement membrane

Conclusions: When administered for 5 days around the time of ovulation, meloxicam decreased the rate of oocyte release without affecting reproductive hormones or menstrual cycle length.

<table>
<tr><th>Species/Strain</th><th>Method of Admin./Vehicle</th><th>Duration of Dosing</th><th>Daily Dose[a] (mg/kg)</th><th>Number/ Sex per Group</th><th>Noteworthy Findings (Meloxicam-Related only)</th></tr>
<tr><td colspan="6">Title: The COX-2 inhibitor meloxicam prevents pregnancy when administered as emergency contraceptive to nonhuman primates. McCann et al. 2013.
Parameters Evaluated: Pregnancy.</td></tr>
<tr><td>Monkey/ Cynomolgus</td><td>Oral/Fruit</td><td>ECM Group: 5 days.
MCM Group: 5 days, 17 days, continuous
See results.</td><td>0 and 0.5</td><td>Varied/ Adult females</td><td>ECM Group: Emergency Contraception Model. Females were treated for 5 days beginning on the day of copulation.
Pregnancy rates: Control = 33.3%; Meloxicam = 6.5%.

MCM Group: Monthly Contraception Model. Females were treated during their menstrual cycles as noted in the table below. Females were housed with males for 5 consecutive days during the female's fertile period.
<table>
<tr><th>Treatment Regimen</th><th>Number of Cycles Resulting in Pregnancy</th><th>Number of Cycles Not Resulting in Pregnancy</th><th>Pregnancy Rate (%)</th></tr>
<tr><td>Cycle Days 5-22</td><td>9</td><td>0</td><td>100</td></tr>
<tr><td>Every Day</td><td>3</td><td>1</td><td>75.0</td></tr>
<tr><td>5 Days During Fertile Period</td><td>5</td><td>1</td><td>83.3</td></tr>
</table>

Conclusions: COX-2 inhibition by meloxicam can prevent pregnancy when administered following a single breeding but is ineffective when used for routine contraception.</td></tr>
<tr><td colspan="6">In Vivo, Embryo-Fetal Developmental Toxicity</td></tr>
<tr><td colspan="6">Title: Impact of anaesthetics and analgesics on fetal growth in the mouse. Thaete et al. 2013.
Parameters Evaluated: Fetal body weight, fetal bone length.</td></tr>
<tr><td>Mouse/C57BL/6J</td><td>IM/Not specified</td><td>Single dose GD 0
2 doses
GD 0 and 1
GD 4 and 5
GD 6 and 7
GD 12 and 13
GD 15 and 16</td><td>0 and 2</td><td>5 to 7/Bred females</td><td>Single dose, GD 0: decreased fetal weight and decrease in length of the humerus.
2 doses: decreased fetal weight and decrease in length of the humerus seen for dams dosed on GD 0 and GD 1.</td></tr>
</table>

<table>
<tr><th>Species/Strain</th><th>Method of Admin./Vehicle</th><th>Duration of Dosing</th><th>Daily Dose[a] (mg/kg)</th><th>Number/ Sex per Group</th><th>Noteworthy Findings (Meloxicam-Related only)</th></tr>
<tr><td colspan="6">Title: Relationship between Cyclooxygenase 1 and 2 selective inhibitors and fetal development with administered to rats and rabbits during the sensitive periods for heart development and midline closure. Cappon et al. 2003.
Parameters Evaluated: Maternal observations, body weight, and food consumption; uterine data; fetal body weight, placental weight, and fetal heart development and midline closure.</td></tr>
<tr><td>Rat/Sprague-Dawley
Rabbit/New Zealand White</td><td>Oral/0.5% MC</td><td>Rats: 2 Doses; GD 9 and 10
Rabbits: 3 Doses; GD 9, 10, and 11</td><td>Rats: 0 and 15
Rabbits: 0 and 600</td><td>20 rats, 18 to 20 rabbits/ Bred females</td><td>Rats: ↓body weight GD 9 to 12.
Rabbits: loose and/or liquid stool, ↓body weight GD 9 to 13, and ↓fetal body weight (9% lower than control fetuses).</td></tr>
</table>

↓ = decrease; CAT = catalase; COX-1 = cyclooxygenase-1; COX-2 = cyclooxygenase-2; FSH = follicle stimulating hormone; GD = Gestation Day; GPx = glutathione peroxidase; GSH = glutathione; hr = hours; LH = luteinizing hormone; IM = intramuscular injection; IP = intraperitoneal injection; MC = methylcellulose; NA = not available/not specified; PC = post-coitus; PGE_1 = prostaglandin E_1; PEG_2 = prostaglandin E_2; $PGF_{2\alpha}$ = prostaglandin $F_{2\alpha}$; SOD = superoxide dismutase; TEST = testosterone;
Gestation Day 0 is defined as the day sperm or sperm plug was found in the vagina.
[a] Meloxicam, unless otherwise specified.

13 References

Ben Maamar M, Lesne L, Hennig K, Desdoits-Lethimonier C, Kilcoyne KR, Coiffec I, Rolland AD, Chevrier C, Kristensen DM, Lavoue V, Antignac JP, Le Bizec B, Dejucq-Rainsford N, Mitchell RT, Mazaud-Guittot S, Jegou B (2017) Ibuprofen results in alterations of human fetal testis development. Sci Rep 7:44184.

Burukoglu D, Baycu C, Taplamacioglu F, Sahin E, Bektur E (2016) Effects of nonsteroidal anti-inflammatory meloxicam on stomach, kidney, and liver of rats. Toxicol Ind Health 32:980-986.

Cappon GD, Cook JC, Hurtt ME (2003) Relationship between cyclooxygenase 1 and 2 selective inhibitors and fetal development when administered to rats and rabbits during the sensitive periods for heart development and midline closure. Birth Defects Res B Dev Reprod Toxicol 68:47-56.

Gaines Das R, North D (2007) Implications of experimental technique for analysis and interpretation of data from animal experiments: outliers and increased variability resulting from failure of intraperitoneal injection procedures. Lab Anim 41:312-320.

Hay-Schmidt A, Finkielman OTE, Jensen BAH, Hogsbro CF, Bak Holm J, Johansen KH, Jensen TK, Andrade AM, Swan SH, Bornehag CG, Brunak S, Jegou B, Kristiansen K, Kristensen DM (2017) Prenatal exposure to paracetamol/acetaminophen and precursor aniline impairs masculinisation of male brain and behaviour. Reproduction 154:145-152.

Hester KE, Harper MJ, Duffy DM (2010) Oral administration of the cyclooxygenase-2 (COX-2) inhibitor meloxicam blocks ovulation in non-human primates when administered to simulate emergency contraception. Hum Reprod 25:360-367.

Inal S, Kabay S, Cayci MK, Kuru HI, Altikat S, Akkas G, Deger A (2014) Comparison of the effects of dexketoprofen trometamol, meloxicam and diclofenac sodium on fibular fracture healing, kidney and liver: an experimental rat model. Injury 45:494-500.

Jaffal SM, Salhab AS, Disi A, Al-Qaadan F (2006) Effects of Meloxicam on Implantation and Parturition of Rat. J Med J 40:88-95.

Kristensen DM, Mazaud-Guittot S, Gaudriault P, Lesne L, Serrano T, Main KM, Jegou B (2016) Analgesic use - prevalence, biomonitoring and endocrine and reproductive effects. Nat Rev Endocrinol 12:381-393.

Marquez-Lara A, Hutchinson ID, Nunez F, Jr., Smith TL, Miller AN (2016) Nonsteroidal Anti-Inflammatory Drugs and Bone-Healing: A Systematic Review of Research Quality. JBJS Rev 4.

Mazaud-Guittot S, Nicolas Nicolaz C, Desdoits-Lethimonier C, Coiffec I, Ben Maamar M, Balaguer P, Kristensen DM, Chevrier C, Lavoue V, Poulain P, Dejucq-Rainsford N, Jegou B (2013) Paracetamol, aspirin, and indomethacin induce endocrine disturbances in the human fetal testis capable of interfering with testicular descent. J Clin Endocrinol Metab 98:E1757-1767.

McCann NC, Lynch TJ, Kim SO, Duffy DM (2013) The COX-2 inhibitor meloxicam prevents pregnancy when administered as an emergency contraceptive to nonhuman primates. Contraception 88:744-748.

Pahlivan B, Cuvas O, Basar H, Bakir F (2010) Comparison of the effects of repeated dose treatments of lornoxicam and meloxicam on renal functions in rats. Comparison of the effects of repeated dose treatments of lornoxicam and meloxicam on renal functions in rats. Turk J Med Sci 40:371-376.
Paksoy Z, Kirbas A (2017) Evaluation of the contraceptive effects of carprofen, flunixin meglumine and meloxicam in rats. Veterinarni Medicina 62:274-278.
Salhab AS, Amro BI, Shomaf MS (2003) Further investigation on meloxicam contraceptivity in female rabbits: luteinizing unruptured follicles, a microscopic evidence. Contraception 67:485-489.
Salhab AS, Gharaibeh MN, Shomaf MS, Amro BI (2001) Meloxicam inhibits rabbit ovulation. Contraception 63:329-333.
Thaete LG, Levin SI, Dudley AT (2013) Impact of anaesthetics and analgesics on fetal growth in the mouse. Lab Anim 47:175-183.
Uzun B, Atli O, Perk BO, Burukoglu D, Ilgin S (2015) Evaluation of the reproductive toxicity of naproxen sodium and meloxicam in male rats. Hum Exp Toxicol 34:415-429.

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/s/

JAY H CHANG on behalf of ARMAGHAN EMAMI
09/20/2018

JAY H CHANG
09/20/2018

RICHARD D MELLON
09/20/2018
I concur.