CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214044Orig1s000

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:	NDA 214044
Supporting document/s:	SDN 1 Original NDA SDN 6 PLLR information SDN 8 Revised label SDN 12 Response to request information (IV risk assessment)
Applicant's letter date:	November 1, 2019, January 27, 2020, February 18, 2020, May 1, 2020
Product:	Qdolo™ (Tramadol Hydrochloride Oral Solution, 25 mg/5 mL)
Indication:	Management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate in adults
Applicant:	Athena Bioscience LLC
Review Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine
Reviewer:	Armaghan Emami, PhD
Team Leader	Jay H. Chang, PhD
Supervisor:	R. Daniel Mellon, PhD
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Executive Summary

1.1 Introduction

NDA 214044 was submitted to seek marketing approval for QDOLO Tramadol Hydrochloride Oral Solution 25 mg/5 mL for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. The NDA was submitted via the 505(b)(2) pathway relying on the Agency's previous finding of safety and efficacy of the listed drug Ultram® (tramadol hydrochloride) tablets for oral use (NDA 20281; approved 3/3/1995). The Applicant has proposed an oral solution for patients who cannot swallow tablets. The proposed maximum recommended daily dose of Tramadol Oral Solution is 400 mg (80 mL)/day, which is the same as the listed drug.

1.2 Brief Discussion of Nonclinical Findings

The Applicant intends to rely on the safety and exposure data of the listed product (Ultram, NDA 20281, 50 mg oral tablet) and the published literature for tramadol, which includes acute and chronic exposure. No nonclinical studies were conducted with the proposed drug product.

All excipients are in FDA-approved products within maximum levels listed in the FDA Inactive Ingredient Database (IID) with the exception of the grape flavoring excipient. The (b) (4) flavoring grape (b) (4) is not listed in the IID. The Applicant obtained a letter of authorization (LOA) to allow FDA to review information in the Type IV drug master file (DMF) (b) (4), which was originally filed in July 2008, for the grape flavor. According to a nonclinical review of DMF (b) (4) dated 4/28/2020, (b) (4) ingredients in the flavor have not been listed in CFR. The concern was conveyed to the Applicant and after a teleconference call with the DMF holder on June 26, 2020, they proposed to (b) (4). On July 8, 2020, the DMF holder submitted an amendment to the DMF indicating that the grape flavor formulation (b) (4) Adequate CFR references were provided for all components; therefore, the formulation is considered acceptable for the intended chronic use.

The components of the container closure system are all food contact compliant, therefore extractable/leachable studies are not needed. An extractable study was conducted by the Applicant and no extractables were detected that would pose a safety concern.

To support the Pregnancy, Lactation, and Females and Males of Reproductive Potential sections of labeling, the Applicant provided a nonclinical literature review that included a summary of 12 relevant published articles (SDN 6; January 27, 2020) that were identified from a literature search. Additional literature searches were conducted by the review team. This review team agrees with the Applicant to include findings from a published article by Aboulhoda et al. (2018) that demonstrated that tramadol administration at doses at or below the maximum recommended human daily dosage

(MRHD) of Tramadol Oral Solution based on BSA comparison to pregnant rats from Gestation Day 10 to 21 caused cerebellar cortex structural abnormalities in rat pups examined postnatally. Although the results are from a single study, there is supportive evidence that supports the conclusion that the findings in this model are likely real and therefore including language in the labeling is justified. In addition, the literature review identified multiple studies suggesting adverse effects on the male reproductive system consistent with and supportive of the current labeling.

Based on the agreed initial Pediatric Study Plan (iPSP) on September 3, 2019, juvenile animal toxicology studies are planned to address potential acute CNS toxicity. A synopsis of the proposed study is provided in the NDA submission. The juvenile animal toxicology studies will be performed concurrently with the planned efficacy, safety, and pharmacokinetic study in pediatric patients 12-17 years of age. These studies may be completed post-approval.

At the Agency's request, the Applicant provided their assessment regarding risks of tramadol OS abuse. We defer to the controlled substance staff (CSS) and the clinical team regarding the adequacy of the intravenous abuse liability assessment for this product. Although the Applicant has concluded that there is low potential for use via the intravenous route, they submitted a toxicological risk assessment for intravenous administration of the drug product formulation components. The risk assessment does not identify adequate data to suggest there is no risk and administration of an oral drug product is likely to result in toxicity because the excipients have not been evaluated for intravenous effects.

1.3 Recommendations

1.3.1 Approvability

From the nonclinical perspective, NDA 214044 may be approved with the recommended labeling revisions and post-marketing requirement for a juvenile animal study.

1.3.2 Additional Non-Clinical Recommendations

The following PMR is recommended:

> Conduct a juvenile animal toxicology study to characterize the impact of tramadol on brain development to support pediatric dosing in adolescent patients 12 to less than 17 years of age.
>
> a. Draft Protocol Submission: August 2020
> b. Final Protocol Submission: November 2020
> c. Study Completion: May 2022
> d. Final Report Submission: March 2023

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. Writings in red are addended by the Applicant to Ultram's label. The final label will be based on further internal discussion and negotiations with the Applicant.

Applicant's Proposed Labeling	Reviewer's Proposed Labeling	Rationale for Reviewer's changes
8.1 Pregnancy **Risk Summary** Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome. Available data with tramadol hydrochloride in pregnant women are insufficient to inform a drug-associated risk for major birth defects and miscarriage.	**8.1 Pregnancy** **Risk Summary** Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome. Available data with tramadol hydrochloride in pregnant women are insufficient to inform a drug-associated risk for major birth defects and miscarriage.	This is consistent with Ultram labeling.
In animal reproduction studies, tramadol administration during organogenesis decreased fetal weights and reduced ossification in mice, rats, and rabbits at 1.4, 0.6, and 3.6 times the maximum recommended human daily dosage (MRHD). Tramadol decreased pup body weight and increased pup mortality at 1.2 and 1.9 times the MRHD [see Data] (b) (4) [redacted] (D) (4)	In animal reproduction studies, tramadol administration during organogenesis decreased fetal weights and reduced ossification in mice, rats, and rabbits at 1.4, 0.6, and 3.6 times the maximum recommended human daily dosage (MRHD). In pre- and post-natal development study, tramadol decreased pup body weight and increased pup mortality at 1.2 and 1.9 times the MRHD [see Data]. In a published study, tramadol caused structural abnormalities in the brains of fetuses when administered to female Sprague Dawley rats from Gestation Days 10-21 at a dose comparable to the MRHD. Based on animal data, advise pregnant women of the potential risk to a fetus.	The Applicant submitted a literature review summarizing published nonclinical studies that investigated effects of tramadol on reproduction, development, and fertility. The Applicant proposed to add a new information (Aboulhoda et al.,2018) to the label based on this review.
(b) (4) [redacted] Based on animal data and (b) (4) [redacted] advise pregnant women of the potential risk to a fetus.		We defer to clinical review team and maternal health team (MHT) for the human risk summary statement. Refer to these clinical reviews for their recommended language. They proposed to remove the changes.

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 U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.	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 U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.	
Data Animal Data Tramadol has been shown to be embryotoxic and fetotoxic in mice, (120 mg/kg), rats (25 mg/kg) and rabbits (75 mg/kg) at maternally toxic dosages, but was not teratogenic at these dose levels. These doses on a mg/m basis are 1.4, 0.6, and 3.6 times the maximum recommended human daily dosage (MRHD) for mouse, rat and rabbit, respectively.	Data Animal Data Tramadol has been shown to be embryotoxic and fetotoxic in mice, (120 mg/kg), rats (25 mg/kg) and rabbits (75 mg/kg) at maternally toxic dosages, but was not teratogenic at these dose levels. These doses on a mg/m basis are 1.4, 0.6, and 3.6 times the maximum recommended human daily dosage (MRHD) for mouse, rat and rabbit, respectively.	No changes recommended. The proposed labeling is identical to the referenced product labeling.
(b) (4) no drug-related teratogenic effects were observed in progeny of mice (up to 140 mg/kg), rats (up to 80 mg/kg) or rabbits (up to 300 mg/kg) treated with tramadol by various routes. Embryo and fetal toxicity consisted primarily of decreased fetal weights, decreased skeletal ossification and increased supernumerary ribs at maternally toxic dose levels. Transient delays in developmental or behavioral parameters were also seen in pups from rat dams allowed to deliver. Embryo and fetal lethality were reported only in one rabbit study at 300 mg/kg, a dose that would cause extreme maternal toxicity in the rabbit. The dosages listed for mouse, rat and rabbit are 1.7, 1.9 and 14.6 times the MRHD, respectively.	(b) (4) . No drug-related teratogenic effects were observed in progeny of mice (up to 140 mg/kg), rats (up to 80 mg/kg) or rabbits (up to 300 mg/kg) treated with tramadol by various routes. Embryo and fetal toxicity consisted primarily of decreased fetal weights, decreased skeletal ossification and increased supernumerary ribs at maternally toxic dose levels. Transient delays in developmental or behavioral parameters were also seen in pups from rat dams allowed to deliver. Embryo and fetal lethality were reported only in one rabbit study at 300 mg/kg, a dose that would cause extreme maternal toxicity in the rabbit. The dosages listed for mouse, rat and rabbit are 1.7, 1.9 and 14.6 times the MRHD, respectively.	The introductory statement is not necessary. The remaining paragraph is identical to the referenced product labeling and therefore acceptable.
(b) (4)	In a published study, oral administration of 50 mg/kg	The Applicant recommended including

(b) (4)	tramadol (1.2 times the MRHD of 400 mg based on BSA comparison) to pregnant female rats from Gestation Day 10-21 caused structural abnormalities in the brains of the offspring.	structural abnormalities on the post-natal cerebellar cortex data from literature review. Data Source: Aboulhoda et al. (2018) We agree with the Applicant to include structural abnormalities on the post-natal brain. However, we recommend modifying the proposed language. Aboulhoda et al. (2018) Since it is not definitive that these nonclinical findings are associated with oxidative stress, we recommend deleting it. See Integrated Summary for discussion of rationale behind this recommendation.
Tramadol was evaluated in pre- and post-natal studies in rats. Progeny of dams receiving oral (gavage) dose levels of 50 mg/kg 1.2 times the MRHD) or greater had decreased weights, and pup survival was decreased early in lactation at 80 mg/kg (1.9 times the MRHD).	Tramadol was evaluated in pre- and post-natal studies in rats. Progeny of dams receiving oral (gavage) dose levels of 50 mg/kg 1.2 times the MRHD) or greater had decreased weights, and pup survival was decreased early in lactation at 80 mg/kg (1.9 times the MRHD).	No changes recommended. The proposed labeling is identical to the referenced product labeling.
8.3 Females and Males of Reproductive Potential Infertility Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible [see Adverse Reactions (6.2)].	**8.3 Females and Males of Reproductive Potential Infertility** Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible [see Adverse Reactions (6.2)]. Published studies in adult male rodents report that tramadol, at clinically relevant doses, can produce adverse effects on male reproductive hormones and tissues [See Nonclinical Toxicology (13.1)].	No changes recommended. The proposed labeling is identical to the referenced product labeling. Data Sources: Primarily based on (Abdellatief, Elgamal, & Mohamed, 2015; Ahmed & Kurkar, 2014; Attia et al., 2018)
12.1 Mechanism of Action TRAMADOL HYDROCHLORIDE ORAL SOLUTION contains	**12.1 Mechanism of Action** TRAMADOL HYDROCHLORIDE ORAL SOLUTION contains	No changes recommended. The proposed labeling is

tramadol, an opioid agonist and inhibitor of norepinephrine and serotonin re-uptake. Although the mode of action is not completely understood, the analgesic effect of tramadol is believed to be due to both binding to μ-opioid receptors and weak inhibition of re-uptake of norepinephrine and serotonin. Opioid activity is due to both low affinity binding of the parent compound and higher affinity binding of the O-demethylated metabolite M1 to μ-opioid receptors. In animal models, M1 is up to 6 times more potent than tramadol in producing analgesia and 200 times more potent in μ-opioid binding. Tramadol-induced analgesia is only partially antagonized by the opioid antagonist naloxone in several animal tests. The relative contribution of both tramadol and M1 to human analgesia is dependent upon the plasma concentrations of each compound [see Clinical Pharmacology (12.2)]. Analgesia in humans begins approximately within one hour after administration and reaches a peak in approximately two to three hours.	tramadol, an opioid agonist and inhibitor of norepinephrine and serotonin re-uptake. Although the mode of action is not completely understood, the analgesic effect of tramadol is believed to be due to both binding to μ-opioid receptors and weak inhibition of re-uptake of norepinephrine and serotonin. Opioid activity is due to both low affinity binding of the parent compound and higher affinity binding of the O-demethylated metabolite M1 to μ-opioid receptors. In animal models, M1 is up to 6 times more potent than tramadol in producing analgesia and 200 times more potent in μ-opioid binding. Tramadol-induced analgesia is only partially antagonized by the opioid antagonist naloxone in several animal tests. The relative contribution of both tramadol and M1 to human analgesia is dependent upon the plasma concentrations of each compound [see Clinical Pharmacology (12.2)]. Analgesia in humans begins approximately within one hour after administration and reaches a peak in approximately two to three hours.	identical to the referenced product labeling.
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility **Carcinogenesis** A slight, but statistically significant, increase in two common murine tumors, pulmonary and hepatic, was observed in an NMRI mouse carcinogenicity study, particularly in aged mice. Mice were dosed orally up to 30 mg/kg in the drinking water (0.36 times the MRHD) for approximately two years, although the study was not done with the Maximum Tolerated Dose. This finding is not believed to suggest risk in humans. No evidence of carcinogenicity was noted in a rat 2-year carcinogenicity study testing oral doses of up to 30 mg/kg in the drinking water, 0.73 times the MRHD.	**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** **Carcinogenesis** A slight, but statistically significant, increase in two common murine tumors, pulmonary and hepatic, was observed in an NMRI mouse carcinogenicity study, particularly in aged mice. Mice were dosed orally up to 30 mg/kg in the drinking water (0.36 times the MRHD) for approximately two years, although the study was not done with the Maximum Tolerated Dose. This finding is not believed to suggest risk in humans. No evidence of carcinogenicity was noted in a rat 2-year carcinogenicity study testing oral doses of up to 30 mg/kg in the drinking water, 0.73 times the MRHD.	No changes recommended. The proposed labeling is identical to the referenced product labeling.

Mutagenesis Tramadol was mutagenic in the presence of metabolic activation in the mouse lymphoma assay. Tramadol was not mutagenic in the in vitro bacterial reverse mutation assay using Salmonella and E. coli (Ames), the mouse lymphoma assay in the absence of metabolic activation, the in vitro chromosomal aberration assay, or the in vivo micronucleus assay in bone marrow.	Mutagenesis Tramadol was mutagenic in the presence of metabolic activation in the mouse lymphoma assay. Tramadol was not mutagenic in the in vitro bacterial reverse mutation assay using Salmonella and E. coli (Ames), the mouse lymphoma assay in the absence of metabolic activation, the in vitro chromosomal aberration assay, or the in vivo micronucleus assay in bone marrow.	No changes recommended. The proposed labeling is identical to the referenced product labeling.
Impairment of Fertility No effects on fertility were observed for tramadol at oral dose levels up to 50 mg/kg in male rats and 75 mg/kg in female rats. These dosages are 1.2 and 1.8 times the maximum recommended human daily dose based on body surface area, respectively.	Impairment of Fertility No effects on fertility were observed for tramadol at oral dose levels up to 50 mg/kg in male rats and 75 mg/kg in female rats. These dosages are 1.2 and 1.8 times the maximum recommended human daily dose based on body surface area, respectively.	No changes recommended. The proposed labeling is identical to the referenced product labeling.
	However, published studies report that treatment of adult male rats with tramadol (40 mg/kg, IP and SC for 30 and 60 days, respectively, 1.2x the MRHD based on BSA; or 4.5 to 135 mg/kg, SC for 18 weeks, 0.01x to 3.2x the MRHD based on BSA) produced adverse effects on male reproductive hormones and male reproductive tissues.	Data Sources: Primarily based on (Abdellatief et al., 2015; Ahmed & Kurkar, 2014; Attia et al., 2018)

2 Drug Information

2.1 Drug

CAS Registry Number: 63282-47-0

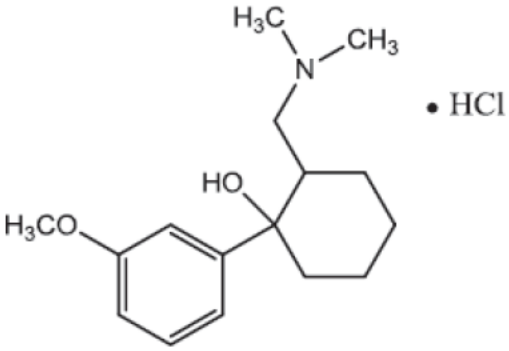
Generic Name: Tramadol hydrochloride

Code Name:

Chemical Name: (1R,2R)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexan-1-ol

Molecular Formula/Molecular Weight: $C_{16}H_{25}NO_2$•HCl/299.84 g/mol

Structure or Biochemical Description



Pharmacologic Class: Opioid agonist

2.2 Relevant INDs, NDAs, BLAs and DMFs

Table 1 Relevant INDs, NDAs, BLAs and DMFs

IND/NDA #	Sponsor	Drug	Status	Date	Indication	Division
IND 127021	Athena Bioscience LLC	Tramadol solution	active	03/29/2018	Moderate to severe pain in adults	DAAP
NDA 20281	Janssen Pharma INC	Ultram tablet	Approved	03/03/1995	Severe pain	DAAP

DMF #	DMF Holder	Product Referenced
(b) (4) Active – 07/10/2008	(b) (4)	(b) (4) (b) (4) grape flavor
(b) (4) Active- 07/27/2007	(b) (4)	Tramadol Hydrochloride

2.3 Drug Formulation

The Applicant has developed Qdolo (tramadol HCl) oral solution for the treatment of (b) (4) pain. The drug product is a clear solution containing 5 mg/mL tramadol HCl USP. The quantitative compositions of the proposed drug products are as follows.

Table 2 Clinical Formulation

Tramadol Hydrochloride Oral Solution, 25 mg/5 mL			
Ingredient	**Weight (mg per 5 mL)**	**% (w/w)**	**Function**
Tramadol Hydrochloride USP	25.000	(b) (4)	Active ingredient
Propylene Glycol USP	(b) (4)		(b) (4)
Glycerin USP			
Sodium Benzoate NF			
Sodium Citrate Dihydrate USP			
Citric Acid USP (b) (4)			
Sucralose (b) (4)			
Grape Flavor (b) (4)			
Purified Water			
Total Per 5 mL		**100%**	

The Applicant has requested a 24-month expiry for the drug product based on the provided 24 months of long-term stability data. The drug product will be stored at controlled room temperature. The reader is referred to the see CMC review for further details.

The maximum daily dose (MDD) of tramadol is 400 mg/day.

2.4 Comments on Novel Excipients

All excipients are in Agency-approved products within approved levels specified in the Inactive Ingredient Database (IID) except for the grape flavor.

Table 3 Applicant's Summary Table of Excipient Concentrations Listed in IID

Tramadol Hydrochloride Oral Solution, 5 mg/mL, Drug Product Formulation, Total Daily Intake, and IID Concentration Summary Table

Raw Materials	(b) (4) Item Number	Amount per Dose (mg)	Total Daily Intake (mg)	Product Concentration (%)	IID Concentration	Referenced Route of Administration
Tramadol HCL, USP	(b) (4)	5.00				(b) (4)
Propylene Glycol, USP						
(b) (4)						
(b) (4)						
Glycerin, USP						
Sodium Benzoate, NF						
Sodium Citrate Dihydrate, USP						
Citric Acid USP (b) (4)						
Sucralose (b) (4) (b) (4)						
Grape Flavor (b) (4) (b) (4)						
Purified Water USP						
Density= (b) (4)						

Table 4 Reviewer's Summary Table of Excipient Evaluation

Ingredient	Quantity (mg/day)	IID maximum potency	Comment on Adequacy for chronic use
Propylene glycol	(b) (4)	Total daily intake (TDI) of up to 18648 mg based on MRHD of approved atypical antipsychotic drug approved for several chronic indications. The WHO acceptable limit for propylene glycol is 25 mg/kg/day based on a 70 kg individual (1750 mg or 1.75 g/day).	Adequate
Glycerin		TDI up to 17696 mg based on MRHD of approved for chronic pain indications.	Adequate
Sodium Benzoate		Sodium Benzoate, has GRAS status and is listed as acceptable in CFR 21 Part §184.1733 and Part§170.3(o)(2) as an antimicrobial agent. The WHO has set an acceptable daily intake limit for sodium benzoate of 0-5 mg/kg bw. For a 70 kg person, the limit would be 350 mg/day.	Adequate
Sodium Citrate Dihydrate		TDI up to 1567.5 mg/75 mL based on MRHD of approved for chronic indications.	Adequate
Citric Acid (b) (4)		839.63 mg	Adequate
Sucralose (b) (4)		Sucralose is listed in the IID. The IID lists a maximum daily exposure of 44 mg as of the date of this review. Sucralose (b) (4) The WHO acceptable daily intake for sucralose has been estimated at up to 15 mg/kg of body weight. For a 70 kg person, the limit would be 1050 mg/day.	Adequate
Grape Flavor (b) (4)		Not listed in the IID DMF Referenced.	Adequate All components in the grape flavoring are supported by CFR information and therefore they are considered safe for the intended chronic use.

The [redacted] flavoring grape [redacted] is not listed in the FDA inactive ingredients database (IID). However, DMF [redacted] has been reviewed and all ingredients in the flavor are acceptable for the proposed use.
There were [redacted] ingredients in the flavor have not been listed in CFR. The concern was conveyed to the Applicant and after a teleconference call with the DMF holder on June 26, 2020, they proposed to [redacted]. On July 8, 2020, they submitted [redacted] with CFR references that was considered acceptable.

2.5 Comments on Impurities/Degradants of Concern

Drug substance:

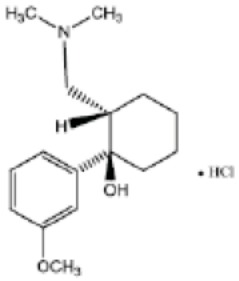
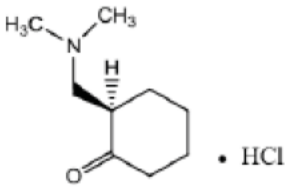
The Applicant proposed the following drug substance specifications:

Table 5 Drug Substance Impurity Specifications

Impurity	Specification	Comment
Tramadol Related Compound A	NMT 0.2%	ICH Q3A qualification threshold is NMT 0.15%. However adequate as per USP (see below)
Related Compound B	NMT [redacted]%	Adequate. Below the ICH Q3A qualification threshold.
Individual Impurities	NMT 0.1%	Adequate. NMT 0.1% is the ICH Q3A identification threshold

Two impurities are listed by [redacted] as present in the manufacturing process of Tramadol Hydrochloride and they are the same impurities listed in the USP. Related Compound A is controlled by USP, [redacted] and [redacted] with a specification of NMT 0.2% using a [redacted] method. Impurity B is controlled by USP, [redacted] with a specification of NMT [redacted] using a [redacted] method. For full details regarding the identification and characterization of impurities, refer to DMF No. [redacted]

Table 6 Drug Substance Impurities

IUPAC Chemical Name	Code No.	Chemical Structure	Process or Degradation Impurity	Source or Mechanism
IUPAC name: (RS,SR)-1-(3-Methoxyphenyl)-2(dimethylaminomethyl-cyclohexanol hydrochloride Other name: **Related compound A**	CAS 73806-49-2		Process impurity	(b) (4)
IUPAC name: (2-[(Dimethylamino)methyl] cyclohexanone hydrochloride) Other name: 2-[(Dimethylamino)methyl] cyclohexanone **Related compound B**	CAS 42036-65-7		Process impurity	

Note that Related Compound A exceeds the ICH Q3A(R2) qualification threshold. However, 0.2% Impurity A is the current specification in DMF (b) (4) that is referenced by numerous approved tramadol drug products. In addition, the specification for Related Compound A of 0.2% is also the current USP specification for this drug substance impurity and as such will be considered acceptable.

Drug product:

The Applicant proposed the following drug product specifications:

Table 7 Drug Product Impurities

Degradant	Stability Specification	Comment
Unspecified Unidentified Degradants	NMT (b) (4)	Adequate. Below the ICH Q3B Identification threshold

There are no specified drug product degradants. For a drug product with an MDD of 400 mg/day, the ICH Q3B identification threshold is (b) (4) % or 2 mg (b) (4) whichever is lower (b) (4) The proposed specifications are acceptable from a nonclinical perspective.

Elemental Impurities:
The Applicant evaluated the final drug product for elemental impurities. There were no elemental impurities that exceeded ICH Q3D Permissible levels for an oral drug product. See the CMC review for further details.

Extractable/Leachable studies
The container closure system for the drug product consists of a 16 oz rectangular high-density polyethylene bottle with a child resistant (b) (4) closure. The components of the container closure system are all food contact compliant, therefore the container closure system is acceptable as per the CMC review team. Although not required, an extractable study was conducted by the Applicant and no extractables were found in the drug product when incubated in the fully assembled closure system. For more detailed see CMC review dated 7/27/2020.

2.6 Proposed Clinical Population and Dosing Regimen

As per the proposed labeling, the Applicant is seeking an indication in adults for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

The initial dosing recommendations propose starting at 25 mg/day and titrating in 25 mg increments every three days to reach 100 mg/day in four divided doses. Thereafter, the total daily dose may be increased by 50 mg doses every three days to reach 200 mg/day (50 mg QID). After titration, doses of 50 to 100 mg can be administered every 4-6 hours with a maximum daily dose of 400 mg/day. See labeling for final dosing recommendations.

2.7 Regulatory Background

The development program for this drug product was completed under IND 127021. PreIND written responses were provided in October of 2015. The IND was originally submitted on March 29, 2018. The Division agreed to the pediatric study plan in 2019. No preNDA meeting was requested.

3 Studies Submitted

3.1 Studies Reviewed

No new GLP toxicology studies were submitted or required to support this 505(b)(2) application.

The Applicant submitted a review and summary of available nonclinical information, including published literature relevant to the tramadol to support the Pregnancy, Lactation, and Females and Males of Reproductive Potential sections of labeling of Tramadol OS (SD 6, 1/27/2020)

In addition, the Applicant submitted a risk assessment of Tramadol oral solution if it were to be misused or abused by the intravenous route of administration: Potential Intravenous Toxicity of Tramadol HCl Oral Solution (25 mg/5 mL) (SD 12, 05/01/2020)

3.2 Studies Not Reviewed

N/A

3.3 Previous Reviews Referenced

N/A

4 Pharmacology

No new nonclinical pharmacology studies were conducted.

5 Pharmacokinetics/ADME/Toxicokinetics

No new absorption, distribution, metabolism, excretion, or other pharmacokinetic drug interaction studies for tramadol have been conducted**.**

6 General Toxicology

No new general toxicology studies have been conducted.

7 Genetic Toxicology

No new genetic toxicology studies were completed. The Applicant is relying upon the data present in the referenced product label.

The referenced drug product label contains the following information:

> Tramadol was mutagenic in the presence of metabolic activation in the mouse lymphoma assay. Tramadol was not mutagenic in the in vitro bacterial reverse mutation assay using Salmonella and E. coli (Ames), the mouse lymphoma assay in the absence of metabolic activation, the in vitro chromosomal aberration assay, or the in vivo micronucleus assay in bone marrow.

8 Carcinogenicity

The Applicant is relying upon the carcinogenicity data in the referenced product label.

The referenced drug product label contains the following information:

> A slight, but statistically significant, increase in two common murine tumors, pulmonary and hepatic, was observed in an NMRI mouse carcinogenicity study, particularly in aged mice. Mice were dosed orally up to 30 mg/kg in the drinking water (0.36 times the MRHD) for approximately two years, although the study was not done with the Maximum Tolerated Dose. This finding is not believed to suggest risk in humans. No evidence of carcinogenicity was noted in a rat 2-year carcinogenicity study testing oral doses of up to 30 mg/kg in the drinking water, 0.73 times the MRHD.

9 Reproductive and Developmental Toxicology

No new reproductive and developmental toxicology studies were conducted with this submission. The Applicant is relying upon the reproductive and developmental toxicology data in the referenced product labeling to address the safety of tramadol.

The referenced drug product labels contain the following information:

> ***Animal Data***
> Tramadol has been shown to be embryotoxic and fetotoxic in mice, (120 mg/kg), rats (25 mg/kg) and rabbits (75 mg/kg) at maternally toxic dosages, but was not teratogenic at these dose levels. These doses on a mg/m^2 basis are 1.4, 0.6, and 3.6 times the maximum recommended human daily dosage (MRHD) for mouse, rat and rabbit, respectively.
>
> No drug-related teratogenic effects were observed in progeny of mice (up to 140 mg/kg), rats (up to 80 mg/kg) or rabbits (up to 300 mg/kg) treated with tramadol by various routes. Embryo and fetal toxicity consisted primarily of decreased fetal weights, decreased skeletal ossification and increased supernumerary ribs at maternally toxic dose levels. Transient delays in developmental or behavioral parameters were also seen in pups from rat dams allowed to deliver. Embryo and fetal lethality were reported only in one rabbit study at 300 mg/kg, a dose that would cause extreme maternal toxicity in the rabbit. The dosages listed for mouse, rat and rabbit are 1.7, 1.9 and 14.6 times the MRHD, respectively.
>
> Tramadol was evaluated in pre- and post-natal studies in rats. Progeny of dams receiving oral (gavage) dose levels of 50 mg/kg 1.2 times the MRHD) or greater had decreased weights, and pup survival was decreased early in lactation at 80 mg/kg (1.9 times the MRHD).
>
> ***Impairment of Fertility***
> No effects on fertility were observed for tramadol at oral dose levels up to 50 mg/kg in male rats and 75 mg/kg in female rats. These dosages are 1.2 and 1.8 times the maximum recommended human daily dose based on body surface area, respectively.

To support the Pregnancy, Lactation, and Females and Males of Reproductive Potential sections of labeling of Tramadol OS, on January 9 and 17, 2020, the Agency requested for review and summary of available nonclinical information, including published literature relevant to the tramadol.

On January 27, 2020, with SD6 submission, the Applicant provided summary of relevant published non-clinical developmental safety data and modified Modules 2, 4, and 5 of the NDA as well as labeling changes.

Literature Overview

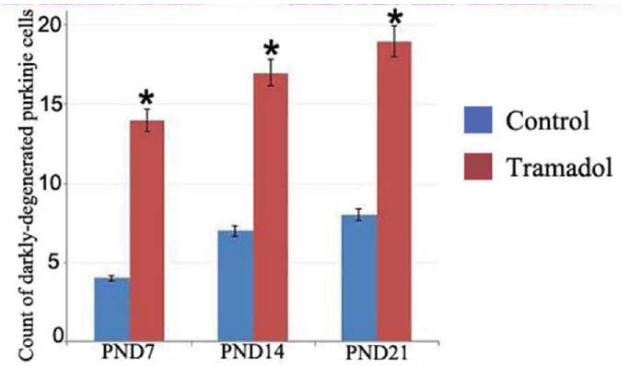
Applicant performed a literature search in PubMed to identify any needed changes in labeling related to pregnancy, lactation, and fertility. Search terms were Tramadol AND (pregnancy OR pregnant OR lactating OR lactation OR fertility), with Species specified as Other Animals and Date Range specified as 01/01/1995 to present. The date range was chosen so that the search would identify all papers meeting the search criteria that were published since the approval of the referenced product ULTRAM® since its 1995 approval. The Applicant determined that a total of nine articles met the search criteria, of which eight provided information relevant to the effects of tramadol on pregnancy, lactation, and fertility. The Applicant proposed to add information to Section 8.1 of labeling based on the published findings of Aboulhoda et al. (2018), which demonstrated adverse effects on developing brain by tramadol. The Applicant's literature review is analyzed and summarized below.

1. **Effect of prenatal tramadol on postnatal cerebellar development: Role of oxidative stress (Aboulhoda & Hassan, 2018)**

In this study (also summarized in the ReproTox database), potential effects of tramadol on fetal development in Sprague Dawley rats were assessed. Twenty pregnant rats were randomized into two groups: a treatment group and a control group. Animals in the treatment group were administered tramadol at 50 mg/kg/day by oral gavage from Gestation Days (GD) 10-21. This dose corresponds to 1.2x the MRHD of 400 mg based on body surface area comparison. Control rats were given saline on the same schedule. Pups were sacrificed on Post-Natal Day (PND) 7. Cerebellar specimens were processed for histomorphometric, immunohistochemical, and electron microscopic assessments and were evaluated for various oxidative stress parameters.

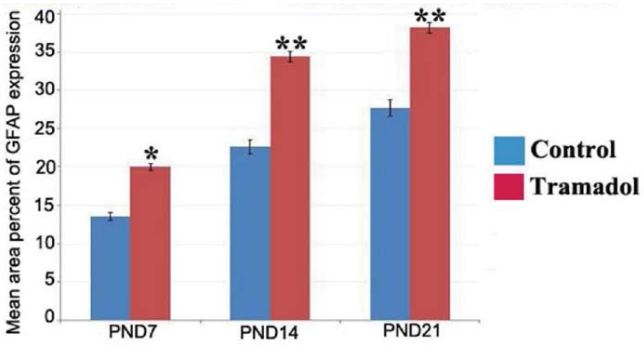
Key findings:
Tramadol administration during pregnancy caused structural abnormalities on the post-natal cerebellar cortex and these were associated with oxidative stress evidenced by elevation of lipid peroxidation products and inhibition of antioxidant enzyme activities.

- Using light microscopic examination, statistically-significant increases in density of darkly-degenerated Purkinje cells were detected in specimens from the tramadol treatment group relative to control. Tramadol-treated Purkinje cells at PND 7 appeared crowded and arranged in multiple layers rather than a single layer, with occasional downward displacement in the granular layer. As hypothesized by the report, neuronal insult could lead to adaptive Purkinje cell crowding as an attempt of Purkinje cells to re-establish novel synaptic contact with other neurons. At PNDs 14 and 21, the Purkinje cells were reported shrunken with densely stained cytoplasm and an irregular outline. According to the authors, the appearance of darkly-degenerated Purkinje cells with markedly condensed cytoplasm and nucleoplasm indicates a pertinent apoptotic response.



- These changes were further confirmed ultrastructurally where the Purkinje neurons showed features of neurodegeneration in the form of chromatin condensation, marked infolding of the nuclear envelope, dilated Golgi channels along with accumulation of secondary lysosomes and lipo-fuschin pigments in tramadol treatments.

- Using immunohistochemical examination, an increase in GFAP (rabbit polyclonal anti-glial fibrillary acidic protein) immuno-reactivity was observed in the cerebellums of the tramadol-treated animals where the Bregmann glial fibers appeared hypertrophied and intensely-stained and the astrocytes in the granular layer exhibited large cell bodies with dense processes indicating activated astroglia. The area percent of GFAP positive immunoreactivity in the tramadol-treated groups was significantly higher than the control group. Astrocyte swelling is a well-known integral reaction to cytotoxic brain injury which was evident in the current work through up-regulation of GFAP immunoreactive astrocytes.



- Tramadol treatment resulted in decrease in the activity of the antioxidant enzymes GSH-Px, CAT and Mn-SOD together with reduction in the level of glutathione and elevation in the level of MDA.

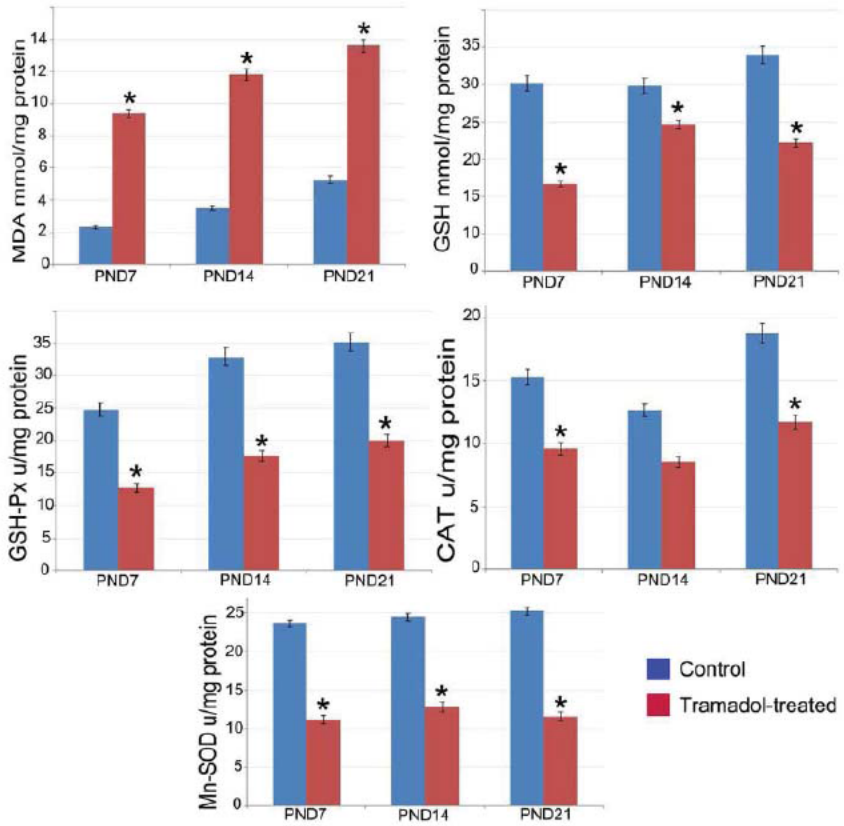


Fig. 11. The mean values of the oxidative markers in the different experimental groups (n = 5 animals in each group, using ANOVA: p value of MDA at PND7 = 0.031, at PND14 = 0.027, at PND21 = 0.029, df = 89, f = 19, p value of GSH at PND7 = 0.031, at PND14 = 0.043, at PND21 = 0.039, df = 89, f = 32, p value of GSH-Px at PND7 = 0.033, at PND14 = 0.03, at PND21 = 0.028, df = 89, f = 27, p value of CAT at PND7 = 0.039, at PND14 = 0.056, at PND21 = 0.022, df = 89, f = 13, p value of Mn-SOD at PND7 = 0.018, at PND14 = 0.024, at PND21 = 0.039, df = 89, f = 37).
*: statistically significant compared to the age-matched controls.

Based on this single paper, the Applicant proposed to add labeling language to the Risk Summary and Data sections of 8.1 Pregnancy section of the package insert to reflect the results of this study. See below the changes they made:

- For the Risk Summary, the Applicant proposes to add the following language indicated in bold font:

  In animal reproduction studies, tramadol administration during organogenesis decreased fetal weights and reduced ossification in mice, rats, and rabbits at 1.4, 0.6, and 3.6 times the maximum recommended human daily dosage (MRHD). Tramadol decreased pup body weight and increased pup mortality at 1.2 and 1.9 times the MRHD *[see Data]*. (b) (4) . Based on animal data and available post-marketing data, advise pregnant women of the potential risk to a fetus.

We defer to the clinical team regarding the acceptability of the human data statement.

- For the *Animal Data* section, the Applicant proposes to add the following language indicated in bold font:

Tramadol has been shown to be embryotoxic and fetotoxic in mice (120 mg/kg), rats (25 mg/kg) and rabbits (75 mg/kg) at maternally toxic dosages but was not teratogenic at these dose levels. These doses on a mg/m^2 basis are 1.4, 0.6, and 3.6 times the maximum recommended human daily dosage (MRHD) for mouse, rat and rabbit, respectively.

(b) (4)

no drug-related teratogenic effects were observed in progeny of mice (up to 140 mg/kg), rats (up to 80 mg/kg) or rabbits (up to 300 mg/kg) treated with tramadol by various routes. Embryo and fetal toxicity consisted primarily of decreased fetal weights, decreased skeletal ossification and increased supernumerary ribs at maternally toxic dose levels. Transient delays in developmental or behavioral parameters were also seen in pups from rat dams allowed to deliver. Embryo and fetal lethality were reported only in one rabbit study at 300 mg/kg, a dose that would cause extreme maternal toxicity in the rabbit. The dosages listed for mouse, rat and rabbit are 1.7, 1.9 and 14.6 times the MRHD, respectively. (b) (4)

Tramadol was evaluated in pre- and post-natal studies in rats. Progeny of dams receiving oral (gavage) dose levels of 50 mg/kg 1.2 times the MRHD) or greater had decreased weights, and pup survival was decreased early in lactation at 80 mg/kg (1.9 times the MRHD).

Reviewer's note:

There are some concerns about this study. In this study, only male pups and only single dose were tested; no maternal toxicities were evaluated; no functional assessments were performed; and no information about the purity of (b) (4) was noted.

However, the study did test a standard SD strain of rat and tested the same dose (50 mg/kg) as employed in the GLP pre- and post-natal studies in rats noted in the label (this dose is equal to MRHD based on body surface area (BSA) comparison). Also, multiple end points to evaluate the CNS structures were employed. See Integrated Summary and Safety Evaluation below for a discussion of why this reviewer believes the findings should be included in labeling.

2. Tramadol in pregnancy and lactation (Bloor, Paech, & Kaye, 2012)

This paper is an overview of the knowledge (as of the 2012 publication date) of the risks associated with the use of tramadol by pregnant and lactating women. In animals key finding below were noted:

- Fertility was found to be unaffected by oral tramadol at doses up to 50 mg/kg in male rats and up to 75 mg/kg in female rats. Embryotoxic and fetotoxic effects were observed in animal studies when doses toxic to the mother were used: double the maximum human dose in mice and rats, and 15 times the maximum human dose in rabbits.

- At lower doses, below those toxic to the adult animal, no fetal toxicity was observed. No teratogenic effects were observed at any dose. Observed toxicity included decreased fetal weight, skeletal ossification and increased supernumerary ribs.

- A study in pregnant ewes given tramadol 100 mg intravenously and intramuscularly demonstrated no effect on maternal mean arterial pressure, maternal heart rate, uterine blood flow, fetal heart rate, fetal mean arterial blood pressure and maternal or neonatal blood gases and acid–base status.

Reviewer's note: The conclusions of this paper are consistent with the current labeling of Ultram. The Ultram label mentions toxicity of the drug at maternally toxic dosages and indicates that no teratogenic effects were observed. Therefore, no updates to the label are recommended based on this published information.

3. Tramadol Reverses the Effects of Neuropathic Pain on Oocyte Maturation and Copulation Ratio in Mice (Dagilgan, Erdogan, & Aksu, 2018)

This study describes the use of tramadol for neuropathic pain in pregnant mice. The study used a peripheral nerve injury model of neuropathic pain in which an incision is made and the sciatic nerve ligated. A total of 80 female mice were used in the study. Of these, 40 were housed with males and 40 were housed only with other females. Each of these 40-mouse groups was further subdivided into four 10-mouse groups: one control group that was neither subjected to surgery nor treated with tramadol; one group subjected to incision but not ligation (sham surgery) and not treated with tramadol; one group subjected to the full surgery but not treated with tramadol; and one group subjected to the full surgery and treated with tramadol. The females housed with males were allowed to mate with the male mice. Efficacy of tramadol against neuropathic pain was tested using the cold-plate latency method, and results indicated that tramadol was effective in alleviating neuropathic pain. Oocytes were collected from all groups.

Key findings:

- No significant differences among the groups in number of total oocytes collected were seen.

- Oocyte maturation was significantly delayed in female mice that underwent the full surgery and were housed with males and not treated with tramadol, whereas mice subjected to the same surgery, treated with tramadol, and housed with males had oocytes that matured at a rate statistically equivalent to the control and sham surgery groups. A similar pattern was seen in copulation rates of the female mice.

- Overall, this study demonstrated that the alleviation of neuropathic pain by tramadol was beneficial to the reproductive potential of female mice.

Reviewer's note: Although interesting, the results of this study suggesting control of pain can reverse the negative impact of pain on the reproductive function in female mice, the study was not designed to test the impact of tramadol alone and the results are not appropriate for labeling.

4. **Pain Medications and Male Reproduction (Drobnis & Nangia, 2017)**

This is a book chapter that provides a survey of available information on the effects of pain medications on male reproduction. The authors indicate that opioids can reduce semen quality, including increased DNA fragmentation. The results are consistent with current labeling of Ultram. The approved Ultram label indicates that *"chronic use of opioids may cause reduced fertility,"* and the results reported in this chapter are consistent with this language. Therefore, no updates to the label are recommended based on this book chapter.

5. **Long-time effects of prenatal morphine, tramadol, methadone, and buprenorphine exposure on seizure and anxiety in immature rats (Gholami et al., 2020)**

This study investigates seizures and anxiety-like behaviors in immature rats prenatally exposed to opioids, simulating the effects of maternal opioid use on offspring. Female rats were mated with males, and pregnant rats were randomized into five administration groups: saline, morphine, tramadol, methadone, and buprenorphine. For the last 7 days of gestation, rats were injected intraperitoneally with increasing doses of the drugs (10, 10, 15, 15, 15, 20, and 20 mg/kg for tramadol). Offspring of the rats were observed and then, on Days 19 and 20 post-partum, tested for anxiety-like behaviors (Day 19) and seizures (Day 20).

Key findings:

- Prenatal exposure to tramadol altered PTZ-induced seizure responses and anxiety-like behaviors in the offspring.
    - Prenatal tramadol prolonged the duration of PTZ-induced seizure behavior in the offspring compared to saline

Table 1. Effects of drugs administration on seizure behavior.

Groups		Time to onset	Tonic-clonic Positive N.	Mean N.	Duration	Death
Saline	Male	144.8 ± 124.4	7/8 (88%)	1.4 ± 0.9	634.4 ± 545	0/8
	Female	292.9 ± 288.8	6/7 (86%)	1.6 ± 1	910 ± 583	1/7 (14%)
Morphine	Male	487.5 ± 207.3#	4/8 (50%)	1.1 ± 1.5	206.1 ± 431.3	0/8
	Female	311.1 ± 83.9	1/7 (14%)&	0.1 ± 0.4$	257.1 ± 680.3	1/7 (14%)
Tramadol	Male	249.7 ± 151	7/8 (88%)	1.5 ± 1.1	905.8 ± 694.9+	0/8
	Female	160 ± 87.6	6/7 (86%)	2 ± 1.6	890.9 ± 532.1	0/7
Bupronorphine	Male	266.4 ± 180	10/12 (83%)	2.6 ± 1.8	417.8 ± 407	0/12
	Female	366.4 ± 368.8	7/12 (58%)	0.8 ± 0.8*	282.3 ± 452.3	1/12 (8%)
Methadone	Male	130 ± 68.2	6/10 (60%)	1.3 ± 1.4	224.3 ± 249.5	0/10
	Female	211.7 ± 172.1	8/12 (67%)	1.5 ± 1.4	332.9 ± 419.5	0/12

*$p < 0.005$ with bupronorphine male.
#$p < 0.005$ with saline and methadone males; + indicates $p < 0.005$ with morphine and methadone males; & indicates $p < 0.05$ with saline, tramadol, and methadone females; $ indicates $p < 0.05$ with saline and methadone females.

- Prenatal tramadol reduced open-arm time in an elevated plus maze in male offspring, suggesting an anxiety-like behavior.

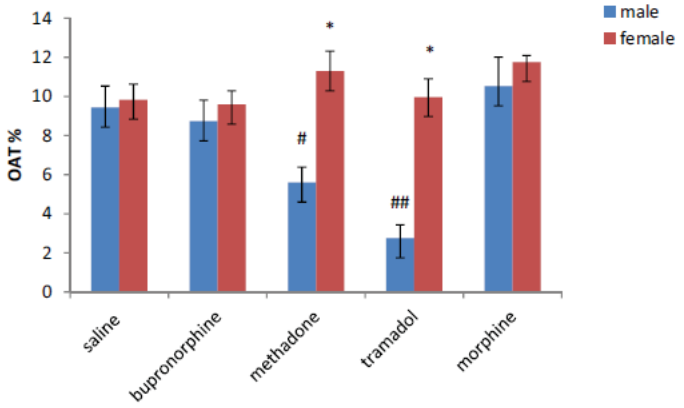


Figure 1. Effects of prenatal drug exposure on the percentage of open arm time (OAT%); The rats were prenatally exposed to the drugs and anxiety-like behaviors assessed at postnatal day 19. Data are expressed as the mean ± SD. #, ## indicate $p < 0.05$ and $p \leq 0.001$ with other male groups except similar symbol; * indicates $p \leq 0.001$ with the same male group.

Reviewer's note: This study in rats showed that use of tramadol in pregnant rats led to seizure and anxiety-like behaviors, which are consistent published studies suggesting prenatal opioids can alter neurochemistry in the offspring. The differential pattern between opioids is interesting and may be the results of the doses tested or the unique pharmacological effect of tramadol on the serotonergic systems in addition to opioid systems. The results are also consistent with conclusion that prenatal opioids may alter the CNS of offspring under the conditions tested. The clinical significance is not clear.

6. **Effect of chronic usage of tramadol on motor cerebral cortex and testicular tissues of adult male albino rats and the effect of its withdrawal: histological, immunohistochemical and biochemical study (Ghoneim, Khalaf, Elsamanoudy, & Helaly, 2014)**

This study showed effects of chronic tramadol usage on motor cerebral cortex and testicular tissues of rats and of the effects of tramadol withdrawal on the rats. Thirty

adult male rats were randomized into three groups: Control Group I (1 mL normal saline 0.9% orally by gavage for 4 weeks), Treatment Group II (50 mg/kg/day tramadol intraperitoneally for 4 weeks; 1.2x the MRHD based on BSA), and Treatment Group III (same dose as Group II, but kept for 4 weeks after dosing to study effects of withdrawal). Animals were sacrificed and their testes and brains studied for the effects of tramadol usage and withdrawal.

Key findings:

- Tramadol-treated animals showed histological abnormalities on both cerebral cortex and testicular tissues, and these abnormalities were associated with oxidative stress. Tissues of tramadol-treated animals also had elevated levels of apoptosis. Tissues of animals four weeks post-treatment (Group III) showed improvement relative to measurements during tramadol treatment, but the parameters did not return to baseline.

Reviewer's note:
Although these studies tested tramadol in adult animals rather than prenatally, the findings in cerebral cortex in the brain suggest the potential for neurotoxicity as suggested by the prenatal study results reported in the Aboulhoda's article (2018).

The findings in testicular tissues are consistent with exiting class labeling for opioids and the current labeling of Ultram under section 8.3 which indicates that "chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible". See Integrated Summary and Safety Evaluation below for a discussion of why this reviewer believes brain and testes findings described in published literature should be included in labeling.

7. Opioids in Breast Milk: Pharmacokinetic Principles and Clinical Implications (Ito, 2018)

There is no nonclinical-related information in this paper to update labeling. This paper is an explanation of the PK exposure of nursing infants to opioids in breast milk and describes the clinical implications of infant opioid exposure through milk. The paper concludes that tramadol may be preferable to other opioids during breastfeeding but that additional studies are required to determine whether tramadol is in fact safer for nursing mothers and their infants.

8. Multiple midline defects identified in a litter of golden retrievers following gestational administration of prednisone and doxycycline: a case series (Kaplan, Gunther-Harrington, Sutton, & Stern, 2018)

This is a case study of developmental defects observed in puppies whose mother was treated with prednisone, doxycycline, and tramadol during pregnancy for immune-

mediated polyarthritis. The puppies were born with multiple midline congenital defects and congenital heart defects; of five puppies analyzed, all had more than one defect. The authors concluded that immunomodulatory therapies should be avoided during the mid-gestational phase of pregnancy in dogs. Because this study involved the administration of multiple drugs, it is impossible to determine which, if any, of the effects were due to tramadol. Therefore, the results are irrelevant to the labeling.

9. The impact of drugs on male fertility: a review (Semet et al., 2017)

This is a review article of the effects of drugs on male fertility. This review cites a paper that associates use of tramadol with delayed ejaculation, sedation, and reduced desire, and mentions another paper that covers the off-label use of tramadol for premature ejaculation. These findings are consistent with current labeling and no changes are recommended.

10. Effect of Tramadol on Rabbit Uterine Contractile Activity Induced in Late Pregnancy (Yakovleva, Nazarova, Prokopenko, & Pavlova, 2017)

This study shows the effect of tramadol infusion on uterine contractile activity in rabbits. Female rabbits were mated. Twenty days later, electrodes to measure uterus electrical activity were aseptically implanted in the rabbits. Two days after electrode implantation (Gestation Day 30), parturition was induced in the rabbits by oxytocin injection. The rabbits were then divided into a tramadol group (1 mL tramadol 5 mg/mL) and a control group (1 mL normal saline), and the test and control treatments were administered 10 minutes after the oxytocin. Labor was then observed and recorded using the implanted electrodes. After delivery, uteri were preserved for further analysis.

Key findings:

Administration of tramadol to rabbits ready for parturition did not alter the number of uterine contractions, but increased phosphocreatine consumption by the myometrium and the amplitude and duration of each contraction. Rabbits not ready for parturition at the time of induction experienced reduction in the amplitude of uterine contractions with tramadol administration.

Reviewer's note: These results are consistent with the labeling of Ultram, which indicates that *"Opioid analgesics, including ULTRAM, can prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions."* Therefore, no changes to the label are recommended.

11. Effects of opioid (tramadol) treatment on testicular functions in adult male rats: The role of nitric oxide and oxidative stress (Ahmed & Kurkar, 2014)

Ahmed and Kurkar administered tramadol (40 mg/kg, SC; 1.2x the MRHD based on BSA) to male rats three times a week for a total of 8 weeks and evaluated the impact on male reproductive tissues. They report that tramadol treatment decreased sperm count and motility, reduced the number of primary spermatocytes, rounded spermatids, and Leydig cells. These changes were correlated with decreased plasma luteinizing hormone, follicle stimulating hormone, testosterone, total cholesterol, and increased prolactin and estradiol levels in plasma. Summaries of these findings are depicted in the images below, reproduced from the publication.

Table 2 Plasma levels of follicle-stimulating hormone, luteinizing hormone, testosterone, estradiol, prolactin and total cholesterol in the control rats and tramadol-treated rats 40 mg/kg per day, three times per week for 8 weeks

	Control	Treated
FSH (mIU/mL)	2.19 ± 0.25	1.49 ± 0.21***
LH (mIU/mL)	2.6 ± 0.35	1.39 ± 0.31***
Tes (ng/mL)	4.21 ± 0.34	3.78 ± 0.52*
E_2 (pg/mL)	42.56 ± 1.92	50.61 ± 8.14**
E_2/T	0.0101 ± 0.0002	0.0134 ± 0.0006
PRL (ng/mL)	6.35 ± 0.44	12.27 ± 0.63***
TCh (mg/dL)	84.73 ± 2.98	74.72 ± 3.07***

E_2, estradiol; E_2/T, estradiol-to-testosterone ratio; FSH, follicle-stimulating hormone; LH, luteinizing hormone; PRL, prolactin; TCh, total cholesterol; Tes, testosterone.

Values are expressed as means ± SD; 20 rats in each group.

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ as compared with the control group.

Table 4 Sperm count and motility in control rats and rats treated with tramadol

	Control	Tramadol
Sperm count (10^6/mL)	68.3 ± 2.54	42.73 ± 1.67***
Sperm motility (%)	87.9 ± 2.01	66.46 ± 2.87***

Values are mean ± SD; 20 rats in each group.

***$P < 0.001$ as compared with the control group.

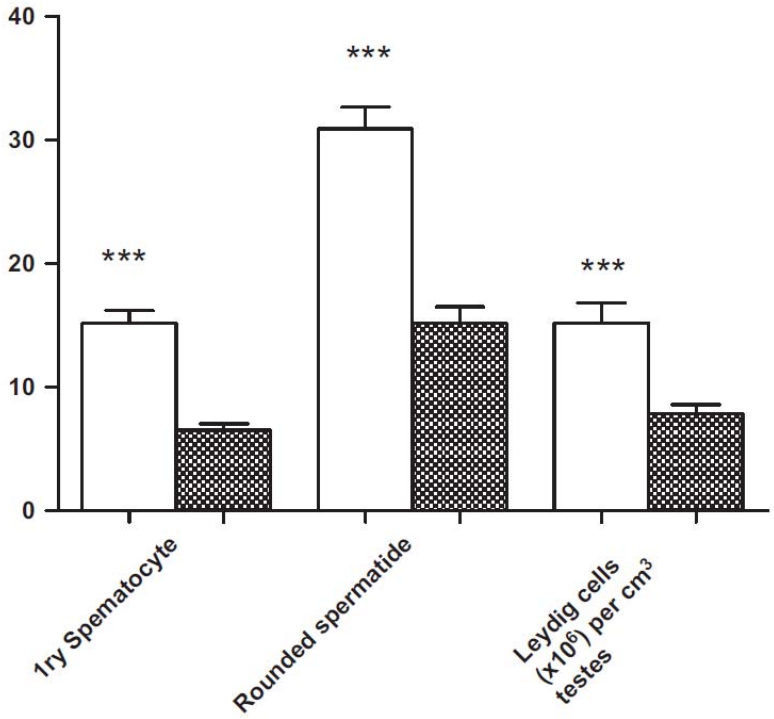


Fig. 1 Effect of tramadol on primary [1ry] spermatocytes, rounded spermatids and leydig cells in control (□) and rats treated with tramadol (▩); 20 rats in each group). ***$P < 0.001$ as compared to treated group.

12. Effects of chronic tramadol administration on testicular tissue in rats: an experimental study (Abdellatief et al., 2015)

In this study the effects of tramadol use were evaluated on testicular tissue in male rats. Adult male rats were treated with tramadol (IP injection of 40 mg/kg; 1.2x the MRHD based on BSA) or saline (control) for 30 days. After 30 days, the animals were sacrificed and analyzed for changes to testicular tissue and hormones in blood.

Key findings:

- Serum luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone were decreased.
- Light microscopy showed degenerative changes in the testes and seminiferous tubules.
- Electron microscopy showed an increase in apoptotic cells, vacuolation, huge lipid droplets and disrupted Sertoli cells. The Leydig cells showed euchromatic nuclei and dilated smooth endoplasmic reticulum.

Reviewer's note: This study showed results consistent with the ability of tramadol to reduce male fertility and provided data on possible mechanisms behind reduction in

fertility. These findings are consistent with the data outlined in the Ultram label which indicates that "*chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible".* See Integrated Summary and Safety Evaluation below for a discussion of why this reviewer believes testes findings described in published literature should be included in labeling.

13. The Effect of Tramadol Treatment on Rat Testes and the Possible Protective Role of Selenium (Light and Electron Microscopic Study) (El Shal & Selim, 2015)

El Shal and Selim treated male albino rats with tramadol (7 mg/rat/day; ~35 mg/kg; ~0.85x the MRHD based on BSA) via gavage and reported adverse histopathological effects of the drug on testes including loss of spermatogenic cells and rare presence of spermatids or sperm and ruptured Leydig cells. However, the paper is not reported in PubMed and is likely a translation found online. The description of the dose tested is unclear and therefore, although consistent with other publications, the results of this study cannot be used to inform labeling.

14. Morphometric and ultrastructural analysis of tramadol effects on epididymis: an experimental study (Attia et al., 2018)

In this study the effects of tramadol use were evaluated on epididymal tissue in rats. Sexually mature male rats (mean 200 g) were treated with control (saline) or various doses of tramadol (0.9, 1.8, 9, 18, 27 mg/day; 4.5, 9, 45, 90, 135 mg/kg; HED of 43.5, 87, 435, 870, 1790 mg/60 kg; 0.1x, 0.2x, 1.1x, 2.1x, 4.5x the MRHD of 400 mg based on BSA) for 18 weeks. After 18 weeks, the animals were sacrificed and their epididymal tissues were analyzed for tramadol-associated changes.

Key findings:

- Histopathology evaluation showed dose-dependent changes including distorted tubular morphology, multiple intercellular and intracellular vacuolation, epithelial disruption, ulceration and/or necrosis, decreased stereocilia, epithelial cell exfoliation and absence of sperm, thickening of the basement membrane, epithelial hyperplasia, tubular epithelial separation from basement membrane, and a decrease in the epididymal duct diameter.

- Electron microscopy of the epididymis showed changes at dose of ≥0.9 mg/day. Changes included a dose-dependent increase in abnormal vacuoles, wide intercellular spaces, thickened irregular basement membrane, irregular outline of principal cells with many lysosomes, distorted mitochondria with abnormal nuclei; decreased stereocilia, and multiple desquamated spermatogenic cells.

The histopathological changes noted are summarized in the table below from the publication suggesting that even the lowest dose tested demonstrated alterations in epididymal tissue.

Table 1. Histopathological and morphological changes in different treated rat groups.

Variable	I No %	II a No %	II b No %	II c No %	II d No %	II e No %	*p* value
Duct number							
Average	5 100	5 100	5 100	5 100	2 40	4 80	0.026*
Decreased	0 00	0 00	0 00	0 00	3 60	1 20	
Duct morphology							
Normal	5 100	5 100	0 00	0 00	0 00	0 00	0.001*
Distorted	0 00	0 00	5 100	5 100	5 100	5 100	
Intracellular vacuolation							
Absent	5 100	1 20	0 00	0 00	1 20	0 00	0.001*
Focal vaculation	0 00	4 80	5 100	1 20	2 40	1 20	
Diffuse vaculation	0 00	0 00	0 00	4 80	2 40	4 80	
Exfoliation in the lumen							
Absent	5 100	5 100	3 60	4 80	2 40	1 20	0.035*
Present	0 00	0 00	2 40	1 20	3 60	4 80	
Epithelial cell necrosis							
Absent	5 100	5 100	5 100	3 60	3 60	4 80	0.224
Focal necrosis	0 00	0 00	0 00	2 40	2 40	1 20	
Clear cell count							
Average	5 100	5 100	5 100	2 40	0 00	0 00	0.003*
Decreased	0 00	0 00	0 00	3 60	3 60	2 40	
Absent	0 00	0 00	0 00	0 00	2 40	3 60	
Stereocillia density							
Absent	0 00	0 00	0 00	0 00	3 60	3 60	0.001*
Average	5 100	0 00	0 00	0 00	0 00	1 20	
Decreased	0 00	5 100	5 100	5 100	2 40	1 20	
Stereocilia morphology							
Normal	5 100	2 40	1 20	0 00	0 00	0 00	0.001*
Distorted	0 00	3 60	4 80	5 100	5 100	5 100	
Interstitial edema							
Absent	5 100	1 20	0 00	0 00	0 00	0 00	0.001*
Present	0 00	4 80	5 100	5 100	5 100	5 100	
Interstitial blood vessels							
Normal	5 100	1 20	0 00	0 00	0 00	0 00	0.001*
Congested	0 00	4 80	5 100	5 100	5 100	5 100	
Interstitial fibrosis							
Absent	5 100	2 40	0 00	0 00	1 20	0 00	0.001*
Present	0 00	3 60	5 100	5 100	4 80	5 100	

*Significant

Reviewer's note:
The results are consistent with current labeling of Ultram which indicates that *"chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible".* However, the paper does report damage to the rat testes after prolonged treatment, findings that are consistent with several other reports noted here. Given the lack of any impact on fertility noted in Section 13 of the current labeling, including a summary statement based on literature would strengthen the existing human risk statement. See Integrated Summary and Safety Evaluation below for a discussion of why this reviewer believes testes findings described in published literature should be included in labeling.

10 Special Toxicology Studies

Studies in Juvenile Animals

The Applicant did not identify any published studies that examined the potential impact of tramadol on the developing brain. Because tramadol is centrally active and the

mechanism of action involves both opioid and serotonin receptors, the Division recommended that a juvenile animal study be completed to characterize the effects of tramadol in the developing brain, unless adequately justified otherwise. The Applicant did not submit any published reports evaluating the potential impact of tramadol on the developing brain. However, in the agreed PSP, the Applicant agreed to conduct a juvenile animal study to support an indication in pediatric patients 12 to < 17 years of age. The Division and PERC agreed that the study may be conducted concurrent with the clinical study. Of note, tramadol is contraindicated in pediatric patients under the age of 12, as such further studies to characterize the effect of tramadol on brain development in children under 12 are not necessary.

During the NDA review cycle, the review team identified published reports that examined the impact of tramadol on the developing offspring.

A study of the neurotoxic effects of tramadol and cannabis in adolescent male albino rats (Nafea, ElKhishin, Awad, & MOhamed, 2016)

Nafea and colleagues administered tramadol (42, 84, and 168 mg/kg/day; HED of 406, 813, 1625 mg/60 kg based on BSA; 1x, 2, and 4x the MRHD) via oral gavage to adolescent male albino rats on the first, second, and third ten days of the study, respectively, beginning on PND 28 to PND 60 (~human brain development from 8 years to 20 years of age as per Semple). Behavior assessments started 4 weeks into the study and a separate group of animals were kept for assessments following a 4-week recovery. Endpoints included sucrose preference test (anhedonia), spatial memory via the Morris water maze, serotonin levels in the cerebral cortex and hippocampus, oxidative stress (as measured by brain malondialdehyde (MDA) and catalase (CAT) levels), and brain histopathology including caspace-3 expression for apoptosis. The authors report that tramadol treatment regimen, increased sucrose preference during treatment but reduced sucrose preference during withdrawal compared to controls. Likewise, tramadol adversely impacted performance on the Morris water maze, an effect that did not show recovery. Tramadol also increased caspase-3 staining during treatment period, an effect that was less evident in the recovery animals, presumably due to clearance of the damaged cells.

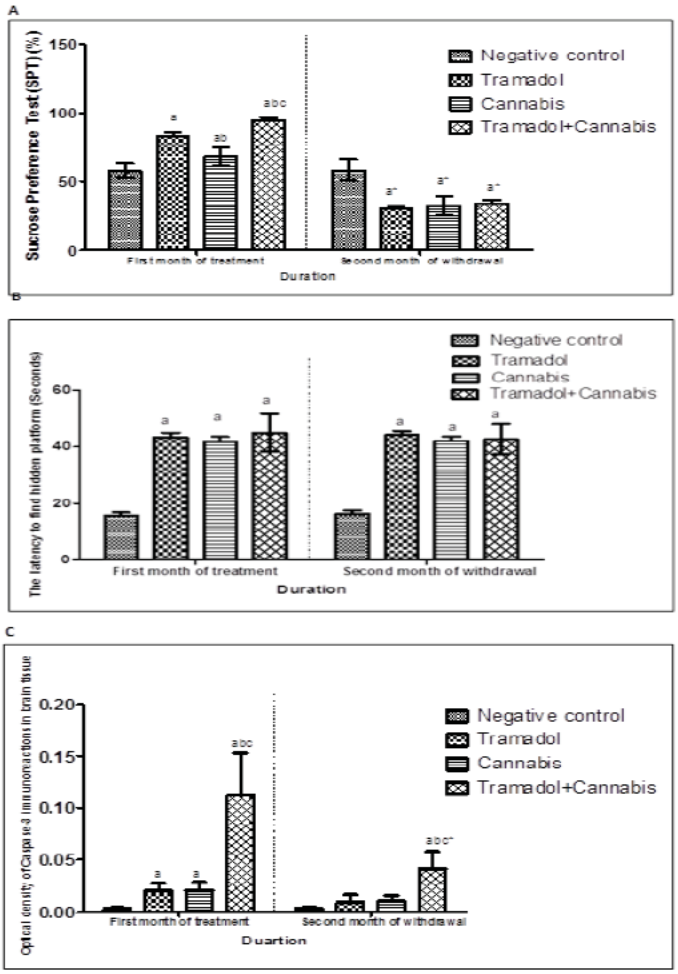


Figure 1: Shows effects of tramadol, cannabis and their combination on behavioral tests (SPT; sucrose preference test, MWM; Morris water maze), (A) sucrose preference and (B) latency to find a hidden platform and (C) the optical density of Caspase–3 immunoreactions in the brain tissue after the first month of treatment and the second month of withdrawal.

In terms of neurochemical changes, tramadol treatment increased cerebral cortex and hippocampus serotonin levels, increased brain MDA levels and decreased CAT levels suggesting oxidative stress. Serotonin levels were decreased in the recovery group compared to controls, however, markers of oxidative stress remained altered, though perhaps recovering, as noted in the table below from the publication.

Table 1: Effects of tramadol, cannabis and their combination on brain biochemical parameters (5–HT, MDA and CAT) after the first month of treatment and the second month of withdrawal.

Parameter	Group	First month of treatment (n=11)	Second month of withdrawal (n=11)
Cerebral cortex& hippocampus 5–HT (µg/mg. tissue)	Negative control	0.87±0.061	0.90±0.061
	TRM	20.99±3.48[a]	0.48±0.11*
	CANN	18.66±3.37[a]	0.42±0.13*
	TRM+CANN	43.54±4.76[abc]	0.45±0.15*
Brain MDA (nmol/g. tissue)	Negative control	0.47±0.05	0.51±0.05
	TRM	18.38±3.64[a]	9.14±2.30[a]*
	CANN	15.48±2.30[ab]	7.16±1.36[a]*
	TRM+CANN	21.36±3.70[abc]	10.04±1.21[ac]*
Brain CAT (U/g)	Negative control	43.21±4.68	43.48±4.67
	TRM	19.65±3.97[a]	35.04±4.74 [a]*
	CANN	21.55±4.45[a]	37.05±4.02 [a]*
	TRM+CANN	15.51±2.93[abc]	34.85±6.29 [a]*

All data were expressed as mean±SD. Two way ANOVA test with Bonferroni post hoc test (significant if $p \leq 0.05$). [a] significant vs negative control group, [b] significant vs TRM, [c] significant vs CANN of the same period (treatment or withdrawal). * Significant vs the same group after the treatment period compared to the withdrawal period (Bonferroni adjusted t–test). TRM; Tramadol, CANN; Cannabis.

Histopathological evidence of neurotoxicity was noted in tramadol treated brains compared to controls as illustrated below:

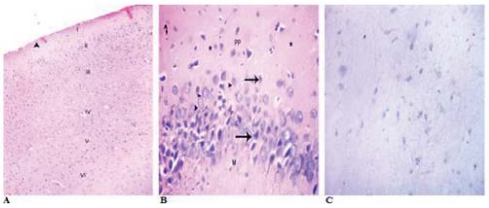


Figure 2: Shows a section of brain of negative control group. Panel (A) shows a delicate layer of pia matter (arrowhead) and the typical layered appearance of the cerebral cortex labelled I–VI as follows: I–Molecular layer; II–External granular layer; III–Pyramidal cell layer; IV–Internal granular layer; V–Ganglionic layer and VI–Multiform layer (H&E × 100). Panel (B) shows normal histo–architecture. Large pyramidal cells (arrows) with basophilic cytoplasm, large vesicular nucleus and long apical dendrite are observed. Granular cells (arrowhead) with large rounded vesicular nuclei are detected. The glial cells (curved arrows) with small dense nuclei are also seen. Note, eosinophilic neutrophil (asterisks) forming the background for the cells. The three layers of the hippocampus, Molecular (M), Pyramidal (P) and Polymorphic (PP), are also shown (H&E ×400). Panel (C) shows the normal negative reaction of brain tissue to the Caspase–3 antibody (Caspase immunostaining ×400).

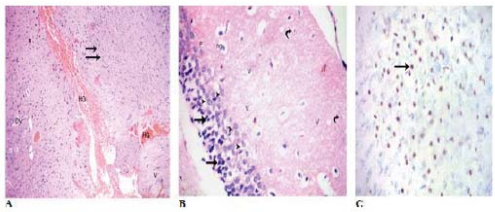
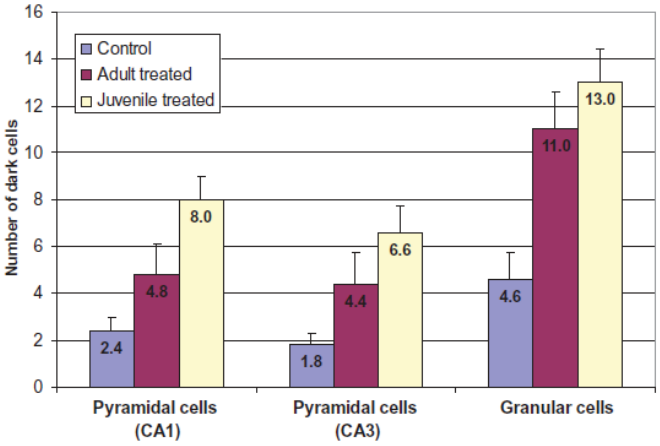


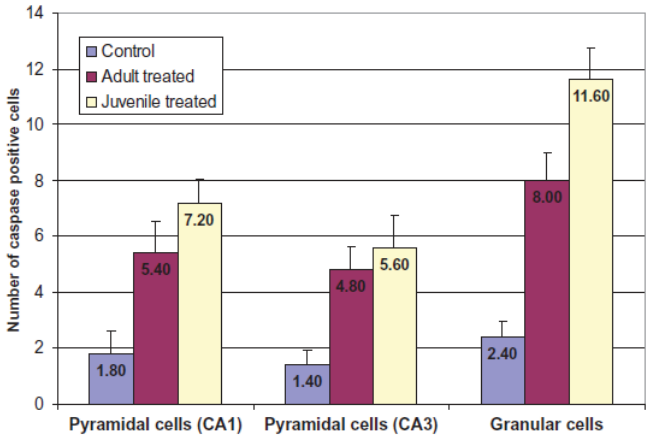
Figure 3: Shows a section of brain of tramadol–treated group. Panel (A) shows neuronal cell disorganization and hypercellularity, as well as increased apoptotic cells (arrows) and dilated blood vessel (DV). Note areas of severe haemorrhage (HG). Vacuolations of neuropil (V) and few red neurons (arrowhead) are evident. (H&E×100). Panel (B) shows marked neuronal degeneration and extensive vacuolations (V). Red neurons (curved arrows) are evident. Few nerve cells have vesicular nuclei (arrowheads). Note glial cells with small nuclei. Increased apoptotic cells in area of the hippocampus (arrows) are observed (H&E ×400). Panel (C) shows many neurons with strong positive reactions to the Caspase–3 antibody in their cytoplasm (Caspase immunostaining ×400).

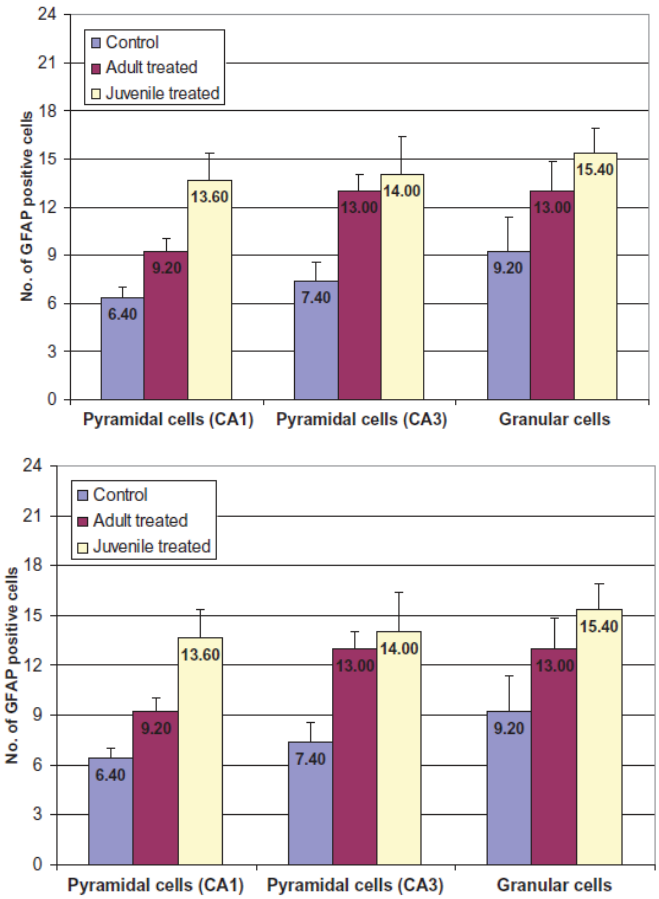
Collectively, these data suggest that tramadol has the potential to alter the CNS resulting in evidence of toxicity. However, the dose escalation paradigm from 1x to 4x the MRDH does complicate interpretation of clinical relevance when the drug is used as indicated. As such, although these data support the conclusion that the drug has the potential to impact the developing CNS, the clinical significance is unclear and more definitive studies are warranted to define a NOAEL.

Tramadol administration induced hippocampal cells apoptosis, astrogliosis, and microgliosis in juvenile and adult male mice, histological and immunohistochemical study (Hussein, Abdel Mola, & Rateb, 2020)

Hussein and colleagues administered tramadol tablets dissolved in water in a dose of 40 mg/kg for 1 month by oral gavage to adult and juvenile Swiss male albino mice (presumably 40 mg/kg tramadol; though the study report is not clear). The study tested the drug product solution on either adult mice (Group II; 3 months old) or juvenile mice (Group III; 3 weeks old). Animals were sacrificed after one month of treatment and perfused brains were examined via light microscopy (H&E stain) and immunohistochemistry for caspase-3 (apoptosis), GFAP (astrocytes), and anti-CD68 (macrophages). Hippocampal slices were also evaluated morphometrically to quantitate the number of DC granule cells and pyramidal neurons in CA3 and CA1, CD68 positive cells, and GFAP positive cells, and via electron microscopy for ultrastructural analysis. Tramadol treatment of adult and juvenile mice produced evidence of degeneration in the hippocampus histologically and as quantified by increase caspace-3, GFAP, and CD68 staining. Juvenile animals appeared to show greater changes suggesting increased vulnerability, as suggested by the figures below, reproduced from the publication.







The dose of 40 mg/kg in the mouse model corresponds to a human equivalent dose of 195 mg/60 kg person (~0.5x the MDD of 400 mg tramadol based on body surface area). These data support the recommendation that definitive studies in an appropriate juvenile animal model should be completed to fully inform the drug product labeling for a pediatric indication.

As documented in the agreed initial Pediatric Study Plan (iPSP) on September 3, 2019, juvenile animal toxicology studies are planned to address potential acute CNS toxicity and will be performed concurrently with the planned efficacy, safety and pharmacokinetic study in pediatric patients 12-17 years of age with PMR. The Applicant submitted a synopsis of a juvenile toxicology protocol (\\cdsesub1\evsprod\nda214044\0001\m1\us\pediatric-study-amend-2.pdf). The Division is currently reviewing that synopsis and will require a complete draft protocol in order to provide recommendations regarding the study design.

Below is the time line for PMR JAS study as noted in the agreed PSP. The dates for the PMRs will be adjusted by three months in order to provide feedback on the study protocol and request a complete draft study protocol.

- Final Protocol Submission: August 2020
- Study Completion: February 2022

- Final Report Submission: December 2022

Risk assessment of Tramadol oral solution if misused or abused by intravenous administration

On April 1, 2020, we sent an IR to the Applicant to provide a risk assessment for their drug product:

"In a recent Advisory Committee (AC) for an oral product containing tramadol, there were concerns raised by the AC members regarding the potential risk of misuse and abuse of the product by the intravenous route. Therefore, we strongly recommend that you be prepared to address this concern. To prepare for this anticipated question, submit a toxicological risk assessment to address the potential toxicities related to the drug product, including both the active and inactive ingredients, should it be administered into the intravascular space. Base the risk assessment on a dose of intravenous tramadol most likely administered intravenously by individuals who misuse tramadol products in this manner."

On May 1, 2020, the Applicant submitted a response to IR related to potential risk of misuse and abuse of Tramadol oral solution by the intravenous route. The Applicant performed a literature analysis to estimate the dose of intravenous tramadol most likely to be used by an individual who misuses tramadol by the intravenous route. A toxicological analysis was also performed to assess the potential toxicities related to the active and inactive ingredients in their drug product based on their estimated dose as determined in the literature analysis.

As per the Applicant, oral tramadol is not expected to be abused by the IV route for several reasons:

1. The primary compound mediating the rewarding effects of tramadol is the M1 metabolite (O-desmethyltramadol), formed in the liver. Parenteral abuse is reduced as first-pass metabolism of M1 is bypassed.

2. The rewarding dose of tramadol via the oral route would require injection of a very large volume, which is not realistic.

    - The typical dose of tramadol abused by the preferred oral route, calculated at 1205 mg, from review of the literature, is irrelevant to this analysis because it would require daily injection of 241 mL of oral solution, an unrealistic scenario.

    - The minimum quantity of tramadol required to achieve a pleasing effect consistent with that sought by abusers has been estimated at 350 mg based on review of multiple studies (Dunn, Bergeria, Huhn, & Strain, 2019). A 350 mg dose, adequate to achieve the opioid effect sought by an abuser, would require injection of 70 mL of Qdolo. Given our maximum estimated injection

volume of 10 mL, an abuser would need to perform seven sequential injections of 10 mL within a short period to achieve a high.

Nonetheless, the Applicant did submit a risk assessment for potential IV misuse. The Applicant's risk assessment estimated that the maximum volume of product that would be abused by an intravenous user on a daily basis would be 60 mL, or 300 mg, divided into six injections of 10 mL (50 mg). This dose estimate was carried forward into the toxicology analysis which was performed by (b) (4). The table below, reproduced from the submission, summarized the Applicant's conclusions.

Table 8 Applicant's Calculated Permitted Daily Exposures for Excipients based on misuse by IV Route

Table 1. Summary of Assessment of Systemic Toxicity			
Component	**Conclusion**	**Total Expected Daily Intake (mg/day)**	**Calculated PDE in 60 kg human (mg/day)**
Tramadol		300	
Propylene glycol	**Systemic toxicity is unlikely based on literature analysis, despite levels exceeding the calculated PDE.**	(b) (4)	(b) (4)
Glycerin	**Systemic toxicity is unlikely based on literature analysis, despite levels exceeding the calculated PDE.**		
Sodium benzoate	**Systemic toxicity is unlikely.**		
Sodium citrate dihydrate	**Systemic toxicity is unlikely.**		
Citric acid (b) (4)	**Systemic toxicity is unlikely.**		
Sucralose, (b) (4) (b) (4)	**Systemic toxicity is possible but cannot be estimated from available information.**		
(b) (4) grape flavor	**Systemic toxicity is unlikely but cannot be accurately assessed based on available information.**		
Purified water	**Systemic toxicity is inconceivable.**		
(b) (4)			

Table 9 Summary of Excipient Levels listed in IID for IV Route

Table 2. Summary of Formulation, Expected Total Daily Intake, and Relevant IID Data					
Compounds	**CAS #**	**Mass per Oral Dose (mg)***	**Expected Intake per Injection (mg)**	**Total Expected Daily Intake (mg/day)**	**Highest FDA IID Entry Per Relevant Route (mg)**
Tramadol	(b) (4)	5	50	300	---
Propylene glycol		(b) (4)	(b) (4)	(b) (4)	(b) (4)
Propylene glycol†					
Glycerin					
Sodium benzoate					
Sodium citrate dihydrate					
Citric acid (b) (4)					
Sucralose, (b) (4) (b) (4)					
(b) (4) rape flavor (b) (4) (b) (4)					
Purified Water					
				(b) (4)	

Reviewer's note: For each of the components, the Applicant performed a literature review to determine the information available on its toxicity, calculated a PDE, performed route-to-route extrapolation as necessary to assess its toxicity by the intravenous route. Although the risk assessment provided was informative, inadequate data have been provided to fully assess risk should the product be administered intravenously. However, because the drug product is not believed to be likely abused by this route (see CSS and MO reviews), more definitive toxicity assessments to inform the potential intravenous risk will not be required.

11 Integrated Summary and Safety Evaluation

The Applicant submitted adequate data to justify the safety of the drug product formulation via the intended route of administration. To update the labeling to conform to PLLR requirements, the Applicant conducted a literature review which identified several reports that appear to expand the current understanding of the toxicity of tramadol. Specifically of note are several reports the suggest tramadol may have adverse effects on developing testes and CNS. Each will be discussed further below.

Effect of Tramadol on Male Reproductive Tissues. Tramadol was studied in a GLP male fertility study in the rat model and there was no evidence of an adverse effect on fertility endpoints in the study as indicated by the referenced product labeling. Several published studies, however, report adverse effects of tramadol on male reproductive

tissues (Abdellatief et al., 2015; Ahmed & Kurkar, 2014; Attia et al., 2018; El Shal & Selim, 2015; Ghoneim et al., 2014). Histopathology data in rodents are likely a more sensitive indicator of potential adverse effects on human male reproductive capacity than fertility studies given the significantly higher fertility of male rats compared to humans. Of note, presumably there were no adverse effects on testicular tissues in the GLP chronic toxicity studies conducted to support the innovator product based on the fact that such findings are not described in the approved referenced product labeling and the drug was approved for use. Of note, current class labeling for opioids does indicate that "chronic use of opioids may cause reduced fertility" based on human data and the proposed labeling contains the statement "Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible." The published nonclinical studies suggest that the effects in males may be due to testicular and epididymal damage and therefore reinforce and elaborate on the conclusions of the existing human data. Likewise, the opioid labels have been updated to include the risk of adverse effects on the endocrine system. Specifically, Section 12 includes the following labeling describing the potential risk related to hypogonadism:

> Effects on the Endocrine System
> Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon *[see Warnings and Precautions (5.11); Adverse Reactions (6)]*.
>
> Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date *[see Adverse Reactions (6)]*.

Given that comparable findings have been reported in multiple separate studies, it seems warranted to include a statement in Sections 13.1 and 8.3 of labeling. For example:

> Section 8.3
>
> Published studies in adult male rodents report that tramadol, at clinically relevant doses, can produce adverse effects on male reproductive hormones and tissues *[See 13.1]*.
>
> Section 13.1
>
> However, published studies report that treatment of adult male rats with tramadol (40 mg/kg, IP and SC for 30 and 60 days, respectively, 1.2x the MRHD based on BSA; or 4.5 to 135 mg/kg, SC for 18 weeks, 0.01x to 3.2x the MRHD based on BSA) produced adverse effects on male reproductive hormones and male reproductive tissues.

Effect of Tramadol on the Developing Brain. Several published reports suggest that prenatal tramadol administration to pregnant animals can have an adverse impact on the developing brain. Specifically, Abdoulhoda and Hassan (2018) reported that treatment of pregnant rats with 1.2x the MRHD of 400 mg (BSA) adverse impacted cerebellar development of male offspring. The endpoints expand upon those that would be tested in the standard pre- and postnatal development studies (PPND). As noted by the referenced product labeling, the only adverse effects noted the offspring at this dose in the GLP PPND study was decreased pup weights; however, it is not clear from the labeling what functional endpoints may have been included in those studies and detailed histopathology of the CNS is not usually conducted in these studies. Of note, decreased pup survival was noted in that study at 1.9x the MRHD already suggesting significant concern for doses between 1.2x and 1.9 the clinical dose. The results of Abhoulhoda and Hassan appear to report more significant adverse effects at a lower exposure than the current labeling. As noted above, the findings from this single study are hard to interpret to inform labeling given the limitations of published studies (e.g., not GLP, only males, single laboratory, no raw data, lack of functional evaluations, single dose). As such, we normally consider the need for additional supportive data to help determine if results from published studies should be considered adequately rigorous and robust to inform labeling. Of the studies noted in this review, we note that Gholami et al. (2020) report that prenatal tramadol treatments at clinically relevant doses altered CNS functional endpoints in the offspring. These effects do not report on the same endpoints as the Abhoulhoda and Hassan study and thus do not show direct replication of the findings. Likewise, Hussein et al. report adverse effects of comparable doses of tramadol on 3-week old animals suggesting the potential impact on the developing brain. However, given the difference in the developmental stage of these animals, this study cannot be considered a replicate of the findings from Abhoulhoda and Hassan either.

The effects reported in both publications may be due to the effects of tramadol on opioid and/or serotonergic systems. There are numerous published studies that suggest that prenatal opioids can have adverse effects on the CNS of the offspring. Many of these findings, even from published literature, are described in the labeling for opioid drug products (e.g., morphine and methadone drug product labeling includes neurochemical changes and neurotoxicity findings that are based entirely on published literature). Recently, published studies reporting adverse effects of oxycodone on the developing CNS have also been included in drug product labels. In contrast to morphine and methadone, there are fewer published studies reporting prenatal effects of tramadol on the developing brain. However, the findings reported in the relatively few tramadol studies to date are consistent with findings already noted in other opioid labeling, which does support their biological plausibility even though only a few papers have been published to date. Including these findings in labeling would help indicate that tramadol is not likely any safer than other opioids in terms of prenatal effects.

Overall, this review team agrees with the Applicant to include structural abnormalities on the post-natal brain. We recommend modifying the proposed language.

Risk summary:

In a published study, structural abnormalities in the brains of offspring were reported when tramadol was administered to pregnant female Sprague Dawley rats from Gestation Day 10-21 at a dose comparable to the MRHD.

Animal data:
In a published study, oral administration of 50 mg/kg tramadol (1.2 times the MRHD of 400 mg based on BSA comparison) to pregnant female rats from Gestation Day 10-21 caused structural abnormalities in the brains of the offspring.

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/s/

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08/21/2020 12:41:45 PM

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08/21/2020 01:27:55 PM

RICHARD D MELLON
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I concur.