CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-123

PHARMACOLOGY REVIEW

MAY - 5 2000

Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products HFD-550

Review and Evaluation of Pharmacology/Toxicology Data

KEY WORDS:	Analgesic
Reviewer Name:	Tracey Zoetis
Division Name:	Anti-inflammatory, Analgesic, and Ophthalmic Drug Products
HFD No.:	HFD-550
Review Completion Date:	5/5/00
IND/NDA number:	NDA 21-123
Serial number/date/type of submission:	Original Submission Letter Date: August 31, 1999 Stamp Date: September 1, 1999
Information to sponsor:	Yes ( ) No (✓)
Related INDs/NDAs/DMFs:	Tramadol: NDA 20-281 (Approved March 3, 1995) Acetaminophen: DMF No [redacted] DMF No. [redacted] Tramadol/Acetaminophen: IND [redacted]
Sponsor:	The R.W. Johnson Pharmaceutical Research Institute 920 Route 202 South, P.O. Box 300 Raritan, New Jersey 08869-0602
Agent:	Not Applicable
Manufacturer for drug substance:	[redacted]

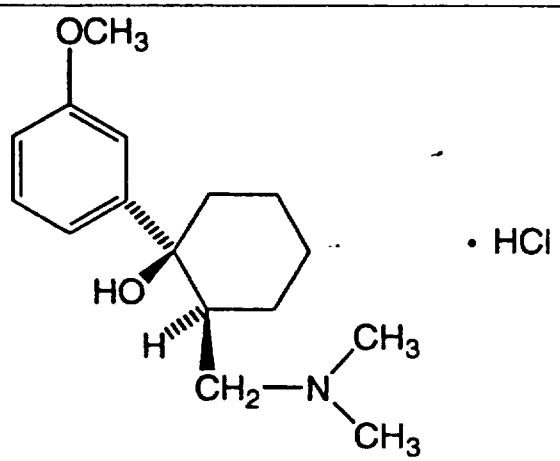
DRUG:

This NDA is for a combination product containing tramadol hydrochloride (37.5 mg) and acetaminophen (325 mg). The following designations have been used to describe 37.5 mg tramadol hydrochloride/325 mg acetaminophen:

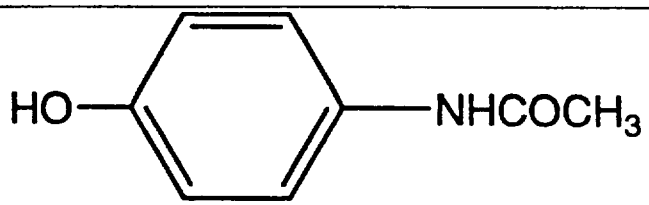
- Tramadol hydrochloride/acetaminophen
- Tramadol HCl/acetaminophen
- Tramadol/acetaminophen
- Tramadol/APAP
- TRAM/APAP
- FD-26898-0020AQ-22.

Identifying information for each drug follows.

Tramadol:

Drug Name:	Tramadol hydrochloride
Class:	Analgesic
CAS Name:	73806-49-2
Code Name:	RWJ-26898-002
Chemical Name:	(±) *cis* -2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride
Structural Formula:	$C_{16}H_{25}NO_2ClH$
Molecular Weight:	299.8
Chemical Structure: Tramadol	

Acetaminophen:

Drug Name:	Acetaminophen
Class:	Analgesic
CAS Name:	103-90-2
Code Name:	None stated
Chemical Name:	N-acetyl-*p*-animophenol
Structural Formula:	C_8H_9NO2
Molecular Weight:	151.17
Chemical Structure: Acetaminophen	

Formulation:

Component	*Function*	*Reference*	*Unit dose (mg/tablet)*
Tramadol Hydrochloride	Active	NDA 20-281	37.50
Acetaminophen, USP	Active	USP	325.00
Powdered Cellulose, NF		NF	
Pregelatinized Starch, NF		NF	
Sodium Starch Glycolate, NF		NF	
Starch, NF		NF	
Purified Water, USP		USP	
Magnesium Sterate, NF		NF	
OPADRY® Light Yellow			
Carnauba Wax, NF		NF	

DISCLAIMER:

Some information in this review may be directly from the Sponsor's submission.

INTRODUCTION AND DRUG HISTORY:

The sponsor is seeking to demonstrate the safety and efficacy of a combination product of 37.5-mg tramadol hydrochloride/ 325-mg acetaminophen, for the management of acute pain. Both active components of the combination product are approved for market in the United States.

The combination of analgesic compounds with different modes or action can sometimes result in a product with an enhanced analgesic effect or reduced side effects. A synergistic interaction between tramadol and acetaminophen was seen in a standard mouse assay that evaluated the oral antinociceptive effects of fixed-ratio tramadol/acetaminophen combination (1:1 through 1:1600). That is, when tramadol and acetaminophen were co administered, significantly less of each component was require to produce a given analgesic effect that would be expected if their effects were merely additive.

When given individually, the conventional oral doses for the two drugs are 50 to 100 mg tramadol every 4 to 6 hours not to exceed 400 mg per day and 500 to 100 mg acetaminophen not to exceed 4000 mg per day. The proposed tramadol/acetaminophen dosage for the treatment of pain is 37.5 mg tramadol hydrochloride and 325 mg acetaminophen per tablet given every 4 to 6 hours not to exceed eight tables in 24 hours. Therefore, for the tramadol/acetaminophen combination, the maximum daily dose of tramadol and acetaminophen is 300 and 2600 mg per day, respectively. Assuming a 50-kg person, this would result in a maximum daily dosage of 6 mg/kg tramadol and 52

mg/kg acetaminophen, which is less than the current dosing limits for the individual components.

STUDIES REVIEWED WITHIN THIS SUBMISSION:

This scope of this review is limited to studies conducted specifically with the tramadol/acetaminophen combination product. These include acute and repeated dose toxicity studies and a teratogenicity study, all of which are listed in the Review Index.

STUDIES NOT REVIEWED WITHIN THIS SUBMISSION:

Preclinical data supporting the approval of tramadol hydrochloride was submitted to NDA 20-281, and was previously reviewed. Similarly, published literature has been the subject of review regarding acetaminophen. These individual products are not the subject of the current review.

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ON ORIGINAL

Review Index

PHARMACOKINETICS/TOXICOKINETICS:

Pharmacokinetic interaction between tramadol and acetaminophen was unique to the dog and is described within the context of the three month repeat dose toxicity study from which the data were obtained.

TOXICOLOGY:

Acute Toxicology:

Acute Oral Safety Study of Tramadol HCl (RWJ-26898-002) Accompanied by Acetaminophen (RWJ-03456-000) in Male Crl:COBS®(WI)BR Rats (vol-3,pp. 203-230)

Study Title:	Acute Oral Safety Study of Tramadol HCl (RWJ-26898-002) Accompanied by Acetaminophen (RWJ-03456-000) in Male Crl:COBS®(WI)BR Rats
Sponsor Study No.:	1419, Report No. DS-90302 (NDA Reference 21)
Study Dates:	February 27, 1990 to March 18, 1990
Report Date:	March 8, 1991
Test Facility:	R.W. Johnson Pharmaceutical Research Institute Spring House, PA
GLP Status:	Compliance with FDA GLP 21CFR 58 indicated.

METHODS

Test Article:	Tramadol HCl 50 mg/ml Acetaminophen 50 mg/ml
Batch No:	Not stated
Purity:	Not stated
Vehicle Control:	[redacted]
Species/Strain:	Rat/Crl:COBS®(WI)BR
Housing:	5/cage on Day 1 and individually thereafter
Route:	Oral gavage
Dose Volume (ml):	Tramadol: 3 ml Acetaminophen: 6 ml
Concentration:	50 mg/ml of each test material
Treatment Schedule:	Single oral dose on Day 1 followed by a 2-week observation period
Observations:	Clinical Signs (daily) Body Weight (prior to treatment and on Days 3, 7, and 14)

Group No.	Treatment	Dose (mg/kg)	No. Males
1	Tramadol HCl	150	5
	HPMC	0	
2	Acetaminophen	300	5
	HPMC	0	
3	Tramadol HCl	150	5
	Acetaminophen	300	
4	HPMC	0	5
5	Tramadol HCl	150	3
	Acetaminophen	300	
6	HPMC	0	3

Note: Treatment Groups 5 and 6 were added subsequent to the start of the study due to a severe head wound induced by cannibalism in a Group 3 animal on Day 1.

RESULTS

Clinical Signs: No treatment-related observations were noted. A severe head wound was inflicted on one Group 3 animal on Day 1 when the animals were group housed. This animal was killed in extremis and treatment Groups 5 and 6 were added to the study.

Body Weight: No treatment-related observations were noted.

Key Study Observations: A single dose of 150 mg/kg tramadol followed by a single dose of 300 mg/kg acetaminophen did not yield any toxicity that is measurable by clinical signs or body weight changes in rats.

Acute Oral Toxicity Study of a Combination of Tramadol and Acetaminophen (APAP) in Rats (Study No. 95013) (vol. 3, pp. 231 – 307)

Study Title:	Acute Oral Toxicity Study of a Combination of Tramadol and Acetaminophen (APAP) in Rats (Study No. 95013)
Sponsor Study No.:	95013 (NDA Reference 22)
Study Dates:	December 5, 1995 – December 19, 1995
Report Date:	February 15, 1996
Test Facility:	R.W. Johnson Pharmaceutical Research Institute Raritan, New Jersey
GLP Status:	Compliance with FDA GLP 21CFR 58 indicated

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THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

30 APR 2001

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products (HFD-550)
Attn.: Document Control Room N115
9201 Corporate Boulevard
Rockville, Maryland 20850

NDA 21-123
ULTRACET™
(37.5 tramadol HCl/325 acetaminophen
Combination Tablets)

CORRESPONDENCE:
Response to FDA Request for Information
Received on 25 April 2001-
Most Common Treatment-Emergent
Adverse Events of 2% or More

Dear Sir/Madam:

Reference is made to NDA 21-123 for ULTRACET™ (37.5 mg tramadol hydrochloride/325 mg acetaminophen) tablets submitted by The R.W. Johnson Pharmaceutical Research Institute (RWJPRI) to the Agency on 31 August 1999, to the FDA action letter for this NDA dated 30 June 2000, and to the RWJPRI Complete Response for the Acute Pain Indication, submitted on 14 November 2000.

Additionally, reference is made to the Agency's request dated 24 April 2001, received via fax on 25 April 2001, for RWJPRI to provide the Cumulative Incidence of the Most Common Treatment-Emergent Adverse Events of 2% or more associated with the active comparator during the first 10 days of Exposure in repeated dose clinical trials of ULTRACET (similar to Table 2 of our proposed label, but also to include the comparator). Additionally, the agency requested a Table with the Cumulative Incidence of Most Common Treatment-Emergent Adverse Events of 2% or more associated with ULTRACET and the active comparator during the first 5 days of Exposure in Repeated Dose Clinical Trials. Our responses are attached herein.

Should you have any questions, please contact me directly at (908) 704-4222 or our phone number dedicated for FDA use at (908) 704-4600.

Sincerely,

Natasha Rogozenski

Natasha Rogozenski
Director
Regulatory Affairs

cc: Yoon Kong, Pharm D. (HFD-550)

ORIGINAL

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N-000 (c

NEW CORRESP

03 MAY 2001

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products (HFD-550)
Attn.: Document Control Room N115
9201 Corporate Boulevard
Rockville, Maryland 20850

NDA 21-123
ULTRACET™
(37.5 tramadol HCl/325 acetaminophen
Combination Tablets)

CORRESPONDENCE:
Response to FDA 2 May 2001 Request
for Information

Dear Sir/Madam:

Reference is made to NDA 21-123 for ULTRACET™ (37.5 mg tramadol hydrochloride/325 mg acetaminophen) tablets submitted by The R.W. Johnson Pharmaceutical Research Institute (RWJPRI) to the Agency on 31 August 1999, to the FDA action letter for this NDA dated 30 June 2000, and to the RWJPRI Complete Response for the Acute Pain Indication, submitted on 14 November 2000.

Additionally, reference is made to a 02 May 2001 e-mail request from Yoon Kong, Pharm D, FDA Project Manager, to Ms. Natasha Rogozenski, RWJPRI, requesting clarification regarding adverse event tables previously submitted on 24 and 27 April 2001. Dr. Kong also requested 3 references that were cited within a reference in the NDA. A reply (including the references) was sent to Dr. Kong via e-mail, and we are hereby submitting the official response to NDA 21-123.

Should you have any questions, please contact me directly at (908) 704-4222 or our phone number dedicated for FDA use at (908) 704-4600.

Sincerely,

Natasha Rogozenski

Natasha Rogozenski
Director
Regulatory Affairs

cc: Yoon Kong, Pharm D. (HFD-550)

ORIGINAL

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ATTACHMENT 3

METHODS

Test Article:	Tramadol (RWJ-26898-002) Acetaminophen (RWJ-03465-000)
Batch No:	Tramadol: [redacted] Acetaminophen: [redacted]
Purity:	Not stated
Vehicle Control:	[redacted]
Species/Strain:	Crl:CD®BR, VAF®/Plus rats
Sample size:	5 sex/group
Housing:	Individual
Route:	Oral gavage
Dose Volume (ml):	See table below
Concentration:	See table below
Dosage (mg/kg/day):	See table below
Treatment Schedule:	Single oral dose on Day 1 followed by a 2-week observation period
Observations:	Clinical Signs (daily) Body Weight (prior to treatment and on Days 4, 8, and 15) Gross Pathology (all rats)

Dose and Concentration for Acute Oral Study in Rats

Group No.	Dose (mg/kg) Tramadol/acetaminophen	Concentration (mg/ml) Tramadol/acetaminophen	Volume (ml/kg)
1	0	0	10
2	100/867.1	15.0/130.0	6.67
3	215/1864.0	21.5/186.4	10
4	275/2384.3	27.5/238.4	10
5	340/2947.8	34.0/294.8	10

RESULTS

Clinical Signs: Mortality was observed during the first three days after dosing at the following incidence: 0/5, 0/5, 1/5, 2/5, and 3/5 males from Groups 1 – 5, respectively, and 0/5, 0/5, 1/5, 4/5, and 4/5 females from Groups 1 – 5, respectively. Prior to death, animals exhibited hypoactivity, increased salivation, decreased respiration rate and were prostrate.

Hypoactivity, few feces, salivation, and nasal and ocular discharge were observed in all treated groups. Other clinical signs noted in Groups 3 – 5 included tremors, prostration, rales, exophthalmia, discolored urine, urine- and feces-stained coat, and straub tail. All surviving animals appeared normal by Day 7, with the majority of clinical signs resolved by Day 4.

Body Weight: Mean body weight values were lower in the treated groups than the control group, beginning on Day 4, however low survival in the Group 4 and 5 females confounds the interpretation of the severity of the body weight effect.

Gross Pathology: Fluid in the stomach, distended urinary bladder, and lung discoloration were observed in rats dying on test. A definitive cause of death was not determined for these animals. There were no treatment-related findings in rats that survived until scheduled necropsy.

Key Study Observations: A single oral dose of tramadol/acetaminophen at levels of 215/1864.0 mg/kg and above resulted in death of some rats under the conditions of this study. The definite cause of death was not determined for animals dying on test. The maximum non-lethal oral dose of tramadol/acetaminophen to rats was 100/867.1 mg/kg under conditions of this study.

Acute Oral Toxicity Study of RWJ-26898-002/RWJ-03456-000 (Tramadol HCl/Acetaminophen) in Beagle Dogs (Study DS95314) (vol. 3, pp. 308 – 385)

Study Title:	Acute Oral Toxicity Study of RWJ-26898-002/RWJ-03456-000 (Tramadol HCl/Acetaminophen) in Beagle Dogs (Study DS95314)
Sponsor Study No.:	DS95314 (NDA Reference 23)
Study Dates:	December 14, 1995 – January 5, 1996
Report Date:	February 13, 1996
Test Facility:	R.W. Johnson Pharmaceutical Research Institute Spring House, Pennsylvania
GLP Status:	Compliance with FDA GLP 21CFR 58 indicated

METHODS

Test Article:	Tramadol (RWJ-26898-002) Acetaminophen (RWJ-03465-000)
Batch No:	Tramadol: [redacted] Acetaminophen: [redacted]
Purity:	Not stated
Vehicle Control:	[redacted]
Species/Strain:	Beagle dog
Sample size:	2/sex/group
Housing:	Individual
Route:	Oral gavage
Dose Volume (ml):	See table below
Concentration:	See table below
Dosage (mg/kg/day):	See table below

Treatment Schedule:	Single oral dose on Day 1 followed by a 2-week observation period
Observations:	Clinical Signs (daily) Body Weight (prior to treatment and on Days 1, 3, 7 and 14) Food Consumption (estimated daily) Gross Pathology (all dogs)

Dose and Concentration for Acute Oral Study in Dogs

Group No.	Dose (mg/kg) Tramadol/acetaminophen	Concentration (mg/ml) Tramadol/acetaminophen	Volume (ml/kg)
1	0	0	2
2	20/173.4	10/86.7	2
3	40/346.8	20/173.4	2
4	60/520.2	30/260.1	2
5	15/130.1	10/86.7	1.5

Note: Group 5 was added due to a clinical sign observed in Group 2.

RESULTS

Clinical Signs: All dogs survived to scheduled necropsy. Decreased activity, increased vocalization, and increased licking were observed in dogs dosed at 20/173.4 mg/kg and greater. Fine tremors were observed on Day 1 in one dog per group administered tramadol/acetaminophen doses of 20/173.4 and 40/346.8 mg/kg, respectively. Coarse tremors, ataxia, cyanosis were observed on Day 1 for dogs administered tramadol/acetaminophen doses of 40/346.8 and 60/520.2 mg/kg, respectively. Clonic convulsions and increased muscle tone and dyspenea were observed in two separate dogs dosed at the 60/520.2-mg/kg level. No treatment-related clinical observations were noted in the 15/130.1-mg/kg-dose group.

Body Weight: No treatment related findings were noted.

Estimated Food Consumption: Food consumption appeared to be low for a single female dog per group administered 40/346.8 and 60/520.2 mg/kg, respectively. When compared to pre-dose food consumption levels, there did not appear to be any effects on food consumption in dogs treated at 20/173.4 mg/kg and below.

Gross Pathology: No treatment related findings were noted.

Key Study Observations: A single oral dose of tramadol/acetaminophen at levels of 20/173.4 mg/kg and above resulted in tremors in some dogs under the conditions of this study. The no observable effect level (NOEL) of tramadol/acetaminophen was 15/130.1 mg/kg, under the conditions of the study. The certainty with which this study can predict acute oral toxicity of the test material in this species is compromised by the low sample size (n=2/sex/group).

Repeated Dose Toxicology:

Four Week Oral Exploratory Toxicity Study of a Combination of Tramadol HCl and Acetaminophen (APAP) in Rats (Study DS95131) (vol. 2, pp. 247 – 315)

Study Title:	Four Week Oral Exploratory Toxicity Study of a Combination of Tramadol HCl and Acetaminophen (APAP) in Rats (Study DS95131)
Sponsor Study No.:	DS95131 (NDA Reference 14)
Study Dates:	Not stated
Report Date:	April 25, 1996
Test Facility:	R.W. Johnson Pharmaceutical Research Institute, Raritan, New Jersey
GLP Status:	Not compliant

METHODS

Test Article:	Tramadol Acetaminophen (APAP)
Batch No:	Not stated for either compound
Purity:	Not stated for either compound
Vehicle Control:	[redacted]
Species/Strain:	CRL:CD®BR, VAF/Plus® Rats
No. of Animals:	5/sex/group
Route:	Oral gavage
Dose Volume:	10 ml/kg
Dosage:	See table below
Treatment Schedule:	Daily for 28 days
Observations:	Clinical Signs (daily) Body Weight (weekly) Food Consumption (weekly) Hematology (Week 4) Serum Chemistry (Week 4) Urinalysis (Week 4) Necropsy (Week 4) Histopathology (Week 4, kidneys and livers from Groups 1 and 4 only)

Dosage

Group	Test Article	Dose (mg/kg)	Concentration (mg/ml)
1	Vehicle	0	0
2	Tramadol/APAP	15/130	1.5/13
3	Tramadol/APAP	30/260	3/26
4	Tramadol/APAP	45/390	4.5/39
5	Tramadol	30	3
6	Tramadol	45	4.5
7	APAP	260	26
8	APAP	390	39

RESULTS

Clinical Signs: The incidence of alopecia and erythema was greater in animals treated with tramadol when compared to controls or animals treated with APAP alone.

Body Weight: Mean body weight values for females treated with 30 and 45 mg/kg tramadol were significantly ($p<0.05$) lower than control at Day 28. There were no treatment-related changes observed in animals treated with APAP alone.

Food Consumption: Rats treated with tramadol consumed slightly less food than those treated with APAP alone or controls. No statistically significant differences were observed.

Hematology: Red blood cell parameters (RBC, MCV, MCHC) and platelets were slightly affected in male rats from the high dose (390 mg/kg) APAP group. Mean values are presented in the following table.

Dose (mg/kg) T=tramadol A=APAP	Males				Females			
	RBC	MCV	MCHC	Platelet	RBC	MCV	MCHC	Platelet
0	8.326	57.28	33.12	839.2	8.110	54.46[T]	35.16	949.6
15 T/130 A	8150	58.88	33.22	796.8	8.084	57.78*	34.50	952.4
30 T/260 A	8.732	57.44	32.92	805.0	8.276	56.82	34.48	907.0
45 T/390 A	8.188	58.52	32.92	889.4	7.936	59.54*	34.06	808.0
30 T	8.340	58.12	32.96	785.6	7.378	56.64	34.68	904.8
45 T	8.348	58.78	33.04	871.8	8.276	56.58	34.60	828.8
260 A	8.400	58.32	32.56	883.6	8.124	57.78*	34.00*	898.0
390 A	7.764	61.18*	32.82	1015	7.892	58.28*	34.08	861.2

*Significantly different from control, $p < 0.05$.
[T]Significant trend across Groups 1, 2, 3, and 4, $p < 0.05$.

Serum chemistry: Alkaline phosphatase levels were slightly lower in males treated with 45/390 mg/kg tramadol/APAP, 45 mg/kg tramadol, and 260- and 390- mg/kg APAP when compared to controls.

Urinalysis: No treatment-related observations were noted.

Necropsy: No treatment-related observations were noted.

Histopathology: No treatment-related observations were noted.

Key Study Observations: The purpose of this study was to provide information to select dose levels for a 3-month study of the tramadol/APAP combination. Based on the clinical signs, body weight gains, and hematological changes the sponsor concluded that the high dose should be 45/390-mg/kg tramadol/APAP and the low dose should be 7.5/65-mg/kg tramadol/APAP.

Three Month Oral Toxicity Study of Tramadol/APAP in Rats (Study 96002) (vol. 4, pp. 1 – 268)

Study Title:	Three Month Oral Toxicity Study of Tramadol/APAP in Rats (Study 96002) (vol. 4, pp. 1 – 268)
Sponsor Study No.:	96002 (NDA Reference 24)
Study Dates:	April 30, 1996 – August 1, 1996
Report Date:	May 15, 1998
Test Facility:	R.W. Johnson Pharmaceutical Research Institute, Raritan, New Jersey
GLP Status:	Compliance with 21 CFR Part 58 indicated.

METHODS

Test Article:	Tramadol (RWJ-26898-002) Acetaminophen (APAP) (RWJ-03465-000)
Batch No:	Tramadol – [redacted] Acetaminophen – [redacted]
Purity:	85 – 120% of label claim, per preclinical release standards
Vehicle Control:	[redacted]
Species/Strain:	CRL:CD®BR, VAF/Plus® Rats
No. of Animals:	10/sex/group
Route:	Oral gavage
Dose Volume:	10 ml/kg/day
Dosage:	See table below
Treatment Schedule:	Daily for 13 weeks
Observations:	Mortality (daily) Clinical Signs (weekly) Body Weight (weekly) Food Consumption (weekly except fasting during weeks 5, 9, and 13) Ophthalmology (predose and Week 12) Hematology (pre dose and Weeks 5, 9, and 13) Serum Chemistry (pre dose and Weeks 5, 9, and 13) Urinalysis (pre dose and Week 5, 9, and 13) Necropsy (Week 14) OrganWeights (Week 14) Histopathology (Week 14, full tissue list [per OECD guidance] for control and high dose Tramadol/APAP groups only; gross lesions from tissues of animals in any group; and tissues with gross lesions from animals dying before scheduled necropsy.)

Dosage

Group	Test Article	Dose (mg/kg)	Concentration (mg/ml)
1	Vehicle	0	0
2	Tramadol/APAP	7.5/65	0.75/6.5
3	Tramadol/APAP	22.5/195	2.25/19.5
4	Tramadol/APAP	45/390	4.5/39.02
5	Tramadol	45	4.5
6	APAP	390	39.02

RESULTS

Mortality: Five rats including 4 males from the vehicle control group and 1 male from the mid dose tramadol/acetaminophen group died during the study. Gross and microscopic evaluation confirmed dosing error as the cause of death for each of the control animals but the cause of death for the Group 3 male was undetermined.

Clinical Signs: The incidence of alopecia was 3/10, 4/10, 6/10, 7/10, 7/10 4/10 for groups 1 – 6 females, respectively.

Body Weight: No treatment-related observations were noted.

Food Consumption: No treatment-related observations were noted.

Ophthalmology: No treatment-related observations were noted.

Hematology: Red blood cell parameters (RBC, MCV, MCHC) and platelets were slightly affected in male rats from the high dose acetaminophen (390 mg/kg) and combination (45/390-mg/kg tramadol/acetaminophen) groups. Mean values are presented in the following table.

Week 13 Red Cell Parameters

Dose (mg/kg) T=tramadol A=APAP	Males		
	RBC	MCV	MCHC
0	8.986[T]	51.40[T]	17.72[T]
7.5 T/65 A	8.985	51.58	17.64
22.5 T/195 A	8.388	52.54	18.16
45 T/390 A	8.484	55.36	19.07*
45 T	9.153	50.86	17.61
390 A	8.080*	55.64	19.33*

*Significantly different from control, $p < 0.05$.
[T]Significant trend across Groups 1, 2, 3, and 4, $p < 0.05$.

Serum chemistry: Potassium concentrations were higher for female rats in the combination groups when compared to controls. Mean potassium concentration values at

Week 13 were 5.37, 6.03*, 6.06*, 6.28*, 5.80, and 5.96 for groups 1 through 6 females, respectively (*=statistically different from control, $p <= 0.05$).

Urinalysis: Slightly higher urine volume values were noted for some female rats from the high dose tramadol, acetaminophen, and tramadol/acetaminophen groups at all study intervals as well as from females in the 22.5/195-mg/kg tramadol/acetaminophen group at Week 13.

Necropsy: No treatment-related observations were noted.

Organ weights: Mean liver weight values for the high dose tramadol/acetaminophen and acetaminophen-only males were significantly higher than values for control males.

Histopathology: No treatment-related observations were noted.

Key Study Observations: Treatment-related findings were observed in clinical signs (alopecia in all groups, increasing in incidence with increasing dose), red cell parameters in the high dose acetaminophen and tramadol/acetaminophen groups, and increased liver weight for high dose tramadol/acetaminophen and acetaminophen-only males. The combination of tramadol and acetaminophen did not appear to effect the toxicity profile of either drug.

Four Week Oral Exploratory Toxicity Range Finding Study of RWJ-26898-002/RWJ30465-000 (Tramadol HCl/Acetaminophen) in Beagle Dogs (Study DS95418) (vol. 3, pp. 1-157)

Study Title:	Four Week Oral Exploratory Toxicity Range Finding Study of RWJ-26898-002/RWJ30465-000 (Tramadol HCl/Acetaminophen) in Beagle Dogs (Study DS95418)
Sponsor Study No.:	DS95418 (NDA Reference 15)
Study Dates:	November 20, 1995 – December 18, 1995
Report Date:	July 18, 1996
Test Facility:	R.W. Johnson Pharmaceutical Research Institute, Raritan, New Jersey
GLP Status:	Not compliant

METHODS

Test Article:	Tramadol Acetaminophen (APAP)
Batch No:	Not stated for either compound
Purity:	Not stated for either compound

Vehicle Control:	[redacted]
Species/Strain:	Beagle Dogs
No. of Animals:	2/sex/group
Route:	Oral gavage
Dose Volume:	1 ml/kg
Dosage:	See table below
Treatment Schedule:	Twice daily for 2 – 4 weeks, as indicated in the table below
Observations:	Clinical Signs (daily) Body Weight (weekly) Food Consumption (estimated daily) Hematology (Weeks –1, 2, and 4) Serum Chemistry (Weeks –1, 2, and 4) Urinalysis (Weeks –2, 2, and 4) Cooximetry (Weeks 2 an 4) Necropsy (Day 15 for Groups 6 and 8; Day 20 for Groups 1, 2, 3, 5, and 7; Group 4 was removed from study on Day 5 due to mortality surviving animals from this group were not necropsied) Organ Weights (liver and kidney) Histopathology (At termination all dogs [except Group 4 survivors removed from study], liver and kidney, and gross changes of uncertain nature) Pharmacokinetics (samples taken from Groups 2, 3, 5, and 7 on Days 1 and 27 prior to dosing and 0.5, 1, 2, 4, 6, 6.5, 7.5, 9.5, and 24 hours after dosing

Dosage

Group	Test Article	Dose (mg/kg/day)	Days Dosed
1	Vehicle	0	28
2	Tramadol/APAP	15/130	28
3	Tramadol/APAP	30/260	28
4	Tramadol/APAP	40/346.8	5
5	Tramadol	30	28
6	Tramadol	40	14
7	APAP	260	28
8	APAP	346.8	14

RESULTS

Clinical Signs: Death occurred on Days 4 and 5 for the two Group 4 females treated with tramadol/APAP at a dose of 40/346.8 mg/kg/day, respectively. One Group 8 female treated with 346.8 APAP alone was killed *in extremis* on Day 8.

The study was not reported in sufficient detail to determine the onset, incidence, or duration of clinical signs; however, the clinical signs present during the course of the study are described.

Notable clinical signs observed in Group 3 animals included decreased activity, tremors, jaundice and discolored urine.

Notable clinical signs observed in Group 4 animals included decreased activity, fine tremors, increased muscle tone, increased vocalization, loss of righting reflex, tonic convulsion, writhing, emesis, fecal occult blood, and respiratory irregularity (rales).

Notable clinical signs observed in Group 5 animals included fine tremors.

Notable clinical signs observed in Group 7 animals included fine tremors fecal occult blood.

Notable clinical signs observed in Group 8 animals included decreased activity, tonic convulsion, jaundice, and discolored urine.

No clinical signs were observed in animals from Groups 2 and 6 and observations for Group 1 were not included in the report.

Body Weight: The study was not reported in sufficient detail to ascertain effects on body weight. A summary paragraph was provided however, no data were included in the report. The sponsor reported that drug related body weight loss occurred in both males and 1 female at 30/260 mg/kg tramadol/acetaminophen and in 1 female at 40/346.8 mg/kg tramadol/acetaminophen. Body weight losses were reported to be associated with decreased food consumption.

Food Consumption: The study was not reported in sufficient detail to ascertain effects on food consumption. Reported body weight losses were attributed to decreased food consumption.

Hematology: Hematology changes were consistent with treatment-related hemolysis and compensatory erythropoesis. The combination groups and the acetaminophen groups generally had lower RBC, hemoglobin, and hematocrit counts and higher MCV, reticulocyte, platelet, and serum and urine bilirubin levels, when compared to controls.

Serum chemistry: Treatment-related increases in liver enzyme levels (ALP, ALT, and GGT) were noted for some dogs treated with 30/260-mg/kg tramadol/acetaminophen, when compared to controls.

Urinalysis: Urine bilirubin levels were slightly higher than controls for the combination groups and the acetaminophen groups. Mean specific gravity and urine color of amber were noted for makes dogs from the mid tramadol/acetaminophen, mid acetaminophen,

Necropsy: Liver weights from the dogs treated with acetaminophen alone and those given the mid dose combination were generally higher than control values. In the animals that died on study, gross observations included yellow livers with an accentuated lobular pattern, tarry contents throughout the gastrointestinal tract, dark urine, and multiple tissues with red discolored areas.

Histopathology: Hepatocellular degeneration and necrosis were observed in the high dosage combination and the high dosage acetaminophen-alone groups. Accumulation of pigment in hepatocytes and/or pigment in tubular epithelial cells of the kidney were observed in the high dose combination-treated animals, 1 high dose acetaminophen-treated female, 1 mid dose acetaminophen-treated male, and 1 male and 1 female in the mid dose combination group. The correlation between the degree of pigment observed by [redacted] staining and iron staining was described as "good" for the mid and high dosage combination groups and the mid and high dose acetaminophen-alone groups. There was positive staining for bilirubin in the mid dosage combination, the high dose combination and the mid and high dose acetaminophen-alone groups.

Key Study Observations: Hepatotoxcity, evidenced by hepatocellular degeneration and necrosis and accumulation of pigment in hepatocytes, was observed in all treated groups of dogs. A no observable effect level was not determined in this study.

Three Month Oral Toxicity Study of RWJ-26898-002/RWJ30465-000 (Tramadol HCl/Acetaminophen) in Dogs (Study DS96303) (vol.7-8, pp. 1 - 754)

Study Title:	Three Month Oral Toxicity Study of RWJ-26898-002/RWJ30465-000 (Tramadol HCl/Acetaminophen) in Dogs (Study DS96303) (vol.7-8, pp. 1 – 754)
Sponsor Study No.:	DS96303 (NDA Reference 25)
Study Dates:	April 22, 1996 – July 26, 1996
Report Date:	February 12, 1999
Test Facility:	R.W. Johnson Pharmaceutical Research Institute, Spring House, Pennsylvania
GLP Status:	Compliance with 21 CFR 58 indicated

METHODS

Test Article:	Tramadol (RWJ-26898-002) Acetaminophen (RWJ-03465-000)
Batch No:	Tramadol: [redacted] Acetaminophen: [redacted]
Purity:	Not stated
Vehicle Control:	[redacted]
Species/Strain:	Beagle Dogs

No. of Animals:	4/sex/group
Route:	Oral gavage
Dose Volume:	1 ml/kg b.i.d.
Dosage:	See table below
Treatment Schedule:	Twice daily (5.5 – 8 hours apart) for 14 weeks
Observations:	Clinical Signs (twice daily) Body Weight (weekly) Food Consumption (estimated daily) Ophthalmology (predose and Week 13) Electrocardiography (predose and Week 13) Physical examinations (predose and Week 13) Hematology (Weeks –4, 5, 9, and 13) Serum Chemistry (Weeks –4, 5, 9, and 13) Urinalysis (Weeks –2, 5, 9, and 13) Drug Absorption (samples collected 0.5, 2, 5, 6, 7.5 and 10.5 hours following the first dose on Days 1 and 89) Necropsy (All dogs dead on test and survivors at Week 14) Organ Weights (adrenal, brain, heart, kidneys, liver, ovaries, pituitary, testes, thyroid from scheduled deaths) Histopathology (At termination; full tissue list in accordance with OECD guidelines control and high dose tramadol/acetaminophen dose groups, and selected tissues [liver gall bladder, kidney, bone marrow, male spleen, male thymus and gross lesions] from all groups)

Dosage

Group	Test Article	Dose (mg/kg/day)
1	Vehicle	0
2	Tramadol/APAP	7.5/65.0
3	Tramadol/APAP	22.5/195.0
4	Tramadol	22.5
5	APAP	195.0

RESULTS

Clinical Signs: One male dog from the high dose tramadol/acetaminophen group was killed *in extremis* on Day 32. Clinical signs included decreased body weight and signs of jaundice and anorexia. All other dogs survived to scheduled termination.

Jaundice was observed, beginning on Day 7 and persisting through Day 45, in dogs administered the high dose combination product. Other clinical signs associated with the administration of the combination product included hunched posture, ataxia, food emesis,

discolored emesis, a lack of feces, pallor, emaciation, urine stained coat, occult blood in the urine, and discolored urine.

Body Weight: Decreases in body weight were observed by Day 36 in dogs administered the high-dose tramadol/acetaminophen combination (22.5/195.0 mg/kg/day) and those administered acetaminophen (195.0 mg/kg/day) or tramadol (22.5 mg/kg/day) alone, when compared to controls and pre-treatment weights.

Food Consumption: Food consumption was generally lower for dogs administered the high-dose tramadol/acetaminophen combination (22.5/195.0 mg/kg/day) and those administered acetaminophen (195.0 mg/kg/day) or tramadol (22.5 mg/kg/day) alone, when compared to controls. The most severely affected dogs were given supplemental diet.

Ophthalmology: No treatment related findings were observed.

Electrocardiography: No treatment related findings were observed.

Physical examinations: No treatment related findings were observed.

Hematology: Hematology changes were consistent with treatment-related hemolysis and compensatory erythropoesis. The high dose tramadol/acetaminophen group and the acetaminophen group generally had lower RBC, hemoglobin, and hematocrit counts and higher MCV, reticulocyte and platelet counts, when compared to controls and pre-treatment values. Hypochromasia and macrocytosis were also observed in these groups. Heinz bodies were observed in one male (high dose acetaminophen) and one female during (high dose combination) during Week 9.

Serum chemistry: Treatment-related increases in liver enzyme (ALP, ALT, and GGT), total bilirubin and triglyceride levels were observed in one or more animals in the high dose combination group and high dose acetaminophen group, when compared to controls or pretreatment values.

Urinalysis: Urine bilirubin and urobilinogen levels were slightly higher than controls for the high dose combination group and the acetaminophen group.

Drug Absorption: Time to maximum concentration (t_{max}) remained relatively constant for all dose and treatment groups for acetaminophen (0.5 hours) and tramadol (6 hours). Dogs were exposed to greater levels of (-) tramadol enantiomer than the (+) tramadol enantiomer, as measured by C_{max} and AUC values after single and multiple oral gavage doses of racemic tramadol administered both alone and in combination with acetaminophen. Single doses of (+) tramadol and (-) tramadol yielded relatively constant mean C_{max} and AUC values when dosed alone and in combination with acetaminophen. Multiple dosing of tramadol alone resulted in a decrease of 81 and 57% in the mean C_{max} value following the second daily for the (+) and (-) enantiomers, respectively. After multiple dosing of tramadol in the high dose combination group (+) tramadol and (-)

tramadol mean C_{max} values following the second daily dose decreased 93 and 66%, respectively. Decreases of 37 and 7% for (+) and (-) tramadol enantiomers were also observed in dogs after multiple dosing of tramadol in the low dose combination product, respectively. Mean AUC values decreased 84 and 89% for (+) tramadol after multiple dosing of tramadol alone and as a high dose combination regimen, respectively. The corresponding decreases of mean AUC values were only 43 and 45% for (-) tramadol after multiple dosing, respectively. After administration of tramadol as a low dose combination product, mean AUC values decreased 50% for (+_ tramadol and increased by 15% for (-) tramadol.

Mean C_{max} and AUC values for acetaminophen remained relatively constant for dogs when comparing single and multiple doses for acetaminophen alone and in combination with tramadol from both combination dose groups. However, mean plasma C_{max} values for acetaminophen following the first daily dose were increased by 108 and 57% in the high dose combination group after single and multiple dosing compared with values from dogs administered acetaminophen alone while 48 and 6.5% increased in mean AUC values were observed following the same dosing regimen.

Necropsy: Gross findings in the high dose tramadol/acetaminophen male dying on test included jaundice and dehydration of all tissues, discolored liver, inspisssated contents of the gall bladder, black foci on the surface of the kidney corresponding to linear rays throughout the cortex, mottled heart atria, and dilatation of the right ventricle and a portion of the vena cava. In dogs killed at termination, particulate material was found in the normal bile in the gall bladder of one male from the low dose combination group and two females from the acetaminophen-only group. Firm, tan to dark foci were observed in the lungs of 1/4, 3/4, and 3/4 female dogs from the high dose combination, tramadol-only, and acetaminophen-only groups.

Mean liver weight values from the high dose combination and the acetaminophen-only groups were higher than control values.

Histopathology: The liver from the high dose tramadol/acetaminophen group that died on study had degeneration and single cell necrosis of hepatocytes with regeneration in periportal areas. Pigmentation of sinusoidal cells, hepatocytes, and vascular cells were also observed and corresponded to the dark discoloration noted grossly. Other findings in this dog included thymic involution, hypercellularity in the bone marrow, pigmentation in the red pulp of the spleen, enteritis in the duodenum, mild testicular degeneration and pigment in various other organs.

Treatment related changes in dogs killed at scheduled termination involved the liver, kidney, spleen, bone marrow, and thymus from dogs treated in the high dose tramadol/acetaminophen and the acetaminophen-alone dose groups.

Liver changes were primarily characterized by pigment accumulation in sinusoidal cells (5/7 dogs in the high dose combination group), bile canaliculi (4/7 dogs in the high dose

combination group and 4/8 dogs in the acetaminophen-only group) and /or hepatocytes (1/7 dogs in the combination group and 6/8 dogs in the acetaminophen-only group). Kidney changes were characterized by brown pigment in the tubular epithelium in 3/4 females from the high dose combination group and 4/4 females from the acetaminophen-only group. Pigment in the red pulp of the spleen was observed in 3/3 and 3/4 males in the high dose combination and acetaminophen-only groups, respectively. Hypercellularity of the bone marrow was observed in 6/7 dogs in the high dose combination group and 5/8 dogs in the acetaminophen-only group.

Key Study Observations: The administration of the high dosage combination of tramadol/acetaminophen (22.5/195 mg/kg/day) resulted in initially altered pharmacokinetics for acetaminophen and subsequent severe hepatotoxicity and lethality. Alterations in acetaminophen pharmacokinetics were less apparent at the end of the study, consistent with a decrease in tramadol blood levels following repeated dosing. Following three months of dosing, the remaining dogs in the high dose tramadol/acetaminophen combination group exhibited a toxicity profile similar to those dogs administered acetaminophen alone. This profile included hepatotoxicity and hemolysis with compensatory erythropoesis. With the exception of increased salivation related to oral dosing, the no observed adverse effect level (NOAEL) for the tramadol/acetaminophen combination was 7.5/65 mg/kg/day, under the conditions of the study.

Overall Toxicology Summary:

The repeated dose toxicity of the combination product was studied in rats and dogs in acute studies and in 4 and 13 weeks. The toxicity associated with the tramadol/acetaminophen combination was similar to that observed for the individual components. Pharmacokinetic interactions unique to the dog caused hepatotoxicity and lethality due to initially elevated plasma acetaminophen levels. This interaction was not evident following multiple dose exposure, due to autoinduction of tramadol metabolism following multiple dose exposure in the dog. This interaction was not observed in rat or man.

CARCINOGENICITY:

Carcinogenicity studies of the combination product have not been performed. The carcinogenic effects of tramadol have been previously studied in support of NDA 20-281. The carcinogenic effects of acetaminophen were studied and reviewed by [redacted] Labeling has been approved for these marketed products.

REPRODUCTIVE TOXICOLOGY:

A study was conducted in female rats to evaluate the developmental toxicity potential of the combination product when administered by oral gavage on Days 6 through 17 of

gestation. The tramadol/acetaminophen combination produced maternal toxicity consisting of dose-related decreases in body weight gains and food consumption in all dose groups. No differences were detected for numbers of corpora lutea, implantations, fetuses, resorptions, or pre-and postimplantion loss. Fetal weights were reduced only for the highest tramadol/acetaminophen dose group. No significant differences were observed for overall external, visceral, and skeletal alterations or specific fetal alterations with the exception of an increased incidence of supernumerary ribs in the 50/434-mg/kg/day-tramadol/acetaminophen group. This is a common variant and not considered a teratogenic response.

REVIEWER SIGNATURE/TEAM LEADER SIGNATURE:

/S/ 7-15-02 /S/ 7/18/02

Tracey Zoetis, M.S.
Pharmacology/Toxicology Reviewer

Pharmacology/Toxicology Team Leader

cc: NDA 21-123
HFD-550/Division Files
HFD-550/PM/ Kong
HFD-550/PT/Zoetis
HFD-550/PT-TL/ Osterberg