Table B2: Demographic and Baseline Characteristics
(All Randomized Subjects; Protocol TRAMAP-ANAG-003)

	TRAM/APAP (N = 50)	TRAM 75 mg (N = 50)	APAP 650 mg (N = 50)	Ibuprofen 400 mg (N = 50)	Placebo (N = 50)	Total (N = 250)
Sex						
Male	22 (44%)	29 (58%)	30 (60%)	29 (58%)	20 (40%)	130 (52%)
Female	28 (56%)	21 (42%)	20 (40%)	21 (42%)	30 (60%)	120 (48%)
Race						
Caucasian	47 (94%)	49 (98%)	47 (94%)	48 (96%)	50 (100%)	241 (96%)
Black	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	1 (<0.5%)
Asian	0 (0%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)	1 (<0.5%)
Other[a]	3 (6%)	1 (2%)	2 (4%)	1 (2%)	0 (0%)	7 (3%)
Age (yr)						
Mean (SD)	19.2 (2.76)	19.2 (3.52)	18.1 (2.36)	18.5 (2.97)	18.8 (2.22)	18.8 (2.81)
Median	18	18	18	18	18	18
Range	16-29	16-33	16-28	16-32	16-24	16-33
Weight (kg)						
Mean (SD)	68.8 (16.43)	69.6 (11.67)	67.8 (13.50)	67.3 (14.08)	66.6 (11.96)	68.0 (13.57)
Median	66	68	67	65	66	66
Range	37-123	45-102	45-105	41-107	50-100	37-123
Height (cm)						
Mean (SD)	173.2 (10.55)	174.9 (8.52)	173.3 (10.66)	175.3 (9.81)	172.1 (9.61)	173.8 (9.85)
Median	173	178	175	173	172	173
Range	140-198	157-188	132-196	155-198	140-196	132-198
Baseline Pain						
Moderate	29 (58%)	34 (68%)	36 (72%)	29 (58%)	39 (78%)	167 (67%)
Severe	21 (42%)	16 (32%)	14 (28%)	21 (42%)	11 (22%)	83 (33%)

[a] Four subjects were Hispanic (two in the APAP 650 mg group, one each in the TRAM/APAP and Ibuprofen 400 mg groups), and one subject each was Spanish (TRAM/APAP), American Indian (TRAM/APAP), and Polynesian (Tramadol 75 mg).

Data source: The sponsor's Table 7 in the report, Page 18

2 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

Appendix C

Data from Study TRAMAP-ANAG-004 AND 005

Table C1: Demographics and Baseline Characteristics
(All Randomized Subjects; Protocol: TRAMAP-ANAG-004)

	TRAM/APAP (N=51)	TRAM 112.5 mg (N=49)	APAP 975 mg (N=50)	Placebo (N=50)	Total (N=200)
Race					
Hispanic	51 (100%)	49 (100%)	50 (100%)	50 (100%)	200 (100%)
Age (years)					
Mean (SD)	26.2 (6.69)	27.1 (7.32)	25.6 (6.09)	27.0 (6.31)	26.5 (6.60)
Median	24	24	25	26	25
Range	18-43	19-49	18-46	18-43	18-49
Weight (kg)					
Mean (SD)	76.1 (16.58)	76.2 (19.31)	72.8 (18.14)	71.9 (16.86)	74.3 (17.72)
Median	73	72	69	69	71
Range	43-114	48-140	42-132	45-118	42-140
Height (cm)					
Mean (SD)	160.7 (6.63)	162.3 (5.79)	160.1 (6.47)	159.4 (8.61)	160.6 (6.98)
Median	160	160	160	160	160
Range	147-175	152-178	150-178	122-180	122-180
Baseline Pain					
Moderate	12 (24%)	7 (14%)	5 (10%)	7 (14%)	31 (16%)
Severe	39 (76%)	41 (84%)	45 (90%)	43 (86%)	168 (84%)
Missing	0	1 (2%)	0	0	1 (1%)

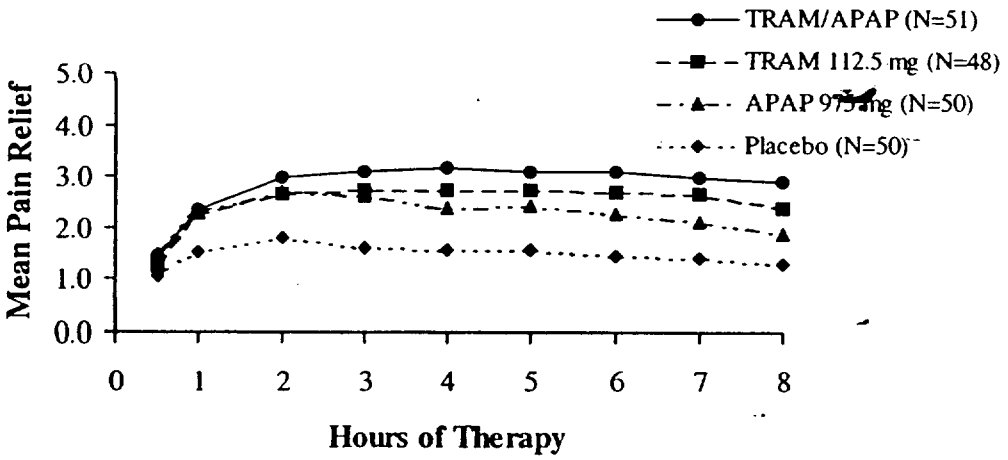
Data source: ANAG-004 report , Page 17

Table C2: Demographics and Baseline Characteristics
(All Randomized Subjects; Protocol TRAMAP-ANAG-005)

	TRAM/APAP (N=50)	Tramadol 112.5 mg (N=50)	APAP 975 mg (N=50)	Placebo (N=50)	Total (N=200)
Sex					
Male	29 (58%)	31 (62%)	28 (56%)	28 (56%)	116 (58%)
Female	21 (42%)	19 (38%)	22 (44%)	22 (44%)	84 (42%)
Race					
Caucasian	38 (76%)	43 (86%)	42 (84%)	46 (92%)	169 (85%)
Black	6 (12%)	1 (2%)	3 (6%)	2 (4%)	12 (6%)
Asian	1 (2%)	0 (0%)	1 (2%)	1 (2%)	3 (2%)
Hispanic	5 (10%)	6 (12%)	4 (8%)	1 (2%)	16 (8%)
Age (yr)					
Mean (SD)	45.4 (12.14)	46.8 (14.63)	42.6 (13.01)	46.9 (15.50)	45.4 (13.38)
Median	45	45	42	44	45
Range	23-78	23-83	20-70	20-83	20-83
Weight (kg)					
Mean (SD)	82.3 (18.31)	86.5 (18.08)	83.7 (18.05)	84.8 (20.43)	84.3 (18.66)
Median	82	89	85	83	84
Range	51-132	47-126	49-125	45-164	45-164
Height (cm)					
Mean (SD)	172.6 (9.06)	174.4 (10.90)	172.3 (9.22)	173.2 (10.44)	173.1 (9.89)
Median	172	178	173	175	173
Range	152-193	152-196	152-193	152-193	152-196
Baseline Pain					
Moderate	41 (82%)	37 (74%)	39 (78%)	41 (82%)	158 (79%)
Severe	9 (18%)	13 (26%)	11 (22%)	9 (18%)	42 (21%)

Data source: ANAG-005 report , Page 18

Figure C1: Mean Pain Relief (PAR) Scores Over Time (Extrapolated)
(Subjects Evaluable for Efficacy; Protocol TRAMAP-ANAG-004)



Pain relief rating scale: 0 = none; 1 = a little; 2 = some; 3 = a lot; 4 = complete

Table C3: Mean Pain Relief (PAR) Scores[a] Over Time (Extrapolated)
(Subjects Evaluable for Efficacy; TRAMAP-ANAG-004)

	Hours								
Treatment	0.50	1	2	3	4	5	6	7	8
TRAM/APAP	1.4 (1.32)	2.3 (1.44)	3.0 (1.24)	3.1 (1.28)	3.2 (1.30)	3.1 (1.35)	3.1 (1.35)	3.0 (1.44)	2.9 (1.44)
	A	A	A	A	A	A	A	A	A
	51	51	51	45	44	44	44	44	41
TRAM 112.5 mg	1.3 (1.14)	2.3 (1.25)	2.6 (1.30)	2.7 (1.38)	2.7 (1.44)	2.7 (1.47)	2.7 (1.46)	2.7 (1.49)	2.4 (1.39)
	A	A	A	A	AB	AB	AB	AB	AB
	48	48	48	43	41	40	38	37	37
APAP 975 mg	1.5 (1.11)	2.3 (1.25)	2.7 (1.23)	2.6 (1.31)	2.4 (1.35)	2.4 (1.42)	2.3 (1.44)	2.1 (1.49)	1.9 (1.42)
	A	A	A	A	B	B	B	B	B
	50	50	50	47	44	39	36	35	33
Placebo	1.0 (1.16)	1.5 (1.31)	1.8 (1.50)	1.6 (1.59)	1.6 (1.61)	1.6 (1.62)	1.5 (1.63)	1.4 (1.59)	1.3 (1.50)
	A	B	B	B	C	C	C	C	C
	50	50	50	38	31	24	21	21	19
P-Value[b]	0.213	0.006	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
RMS Error	1.185	1.316	1.322	1.394	1.429	1.465	1.473	1.504	1.439

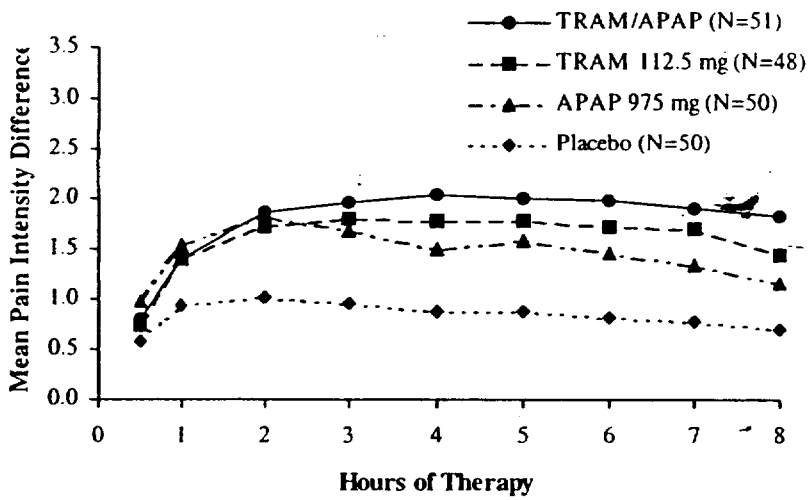
[a] Treatment means with a common letter (i.e., A,B,C,D) are not significantly different by Fisher's LSD at a level of 0.05. For each treatment group mean (*SD*), the number of subjects remaining in the trial is displayed at each time point.

[b] Statistically significant difference among all treatment groups at $p \leq 0.05$, F-test.

Pain relief scale: 0=none; 1=a little; 2=some; 3=a lot; 4=complete.

Data source: ANAG-004 report , Page 21

Figure C2: Mean Pain Intensity Difference (PID) Scores Over Time (Extrapolated)
(Subjects Evaluable for Efficacy; Protocol TRAMAP-ANAG-004)



Pain intensity rating scale: 0 = none; 1 = mild; 2 = moderate; 3 = severe.

Table C4: Mean Pain Intensity Differences (PID) Scores[a] Over Time (Extrapolated)
(Subjects Evaluable for Efficacy; TRAMAP-ANAG-004)

	Hours								
Treatment	0.50	1	2	3	4	5	6	7	8
TRAM/APAP	0.8 (0.78)	1.4 (0.98)	1.9 (0.96)	2.0 (0.98)	2.0 (1.02)	2.0 (1.04)	2.0 (1.05)	1.9 (1.10)	1.8 (1.11)
	AB	A	A	A	A	A	A	A	A
	51	51	51	45	44	44	44	44	41
TRAM 112.5 mg	0.8 (0.70)	1.4 (0.96)	1.7 (1.01)	1.8 (1.09)	1.8 (1.17)	1.8 (1.19)	1.7 (1.18)	1.7 (1.20)	1.4 (1.13)
	AB	A	A	A	AB	A	AB	AB	AB
	48	48	48	43	41	40	38	37	37
APAP 975 mg	1.0 (0.68)	1.5 (0.89)	1.8 (0.92)	1.7 (0.98)	1.5 (0.97)	1.6 (1.01)	1.5 (1.01)	1.3 (1.10)	1.2 (1.04)
	A	A	A	A	B	A	B	B	B
	50	50	50	47	44	39	36	35	33
Placebo	0.6 (0.81)	0.9 (0.87)	1.0 (1.02)	1.0 (1.12)	0.9 (1.14)	0.9 (1.15)	0.8 (1.19)	0.8 (1.15)	0.7 (1.11)
	B	B	B	B	C	B	C	C	C
	50	50	50	38	31	24	21	21	19
P-Value[b]	0.065	0.009	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
RMS Error	0.745	0.925	0.976	1.044	1.077	1.100	1.110	1.137	1.096

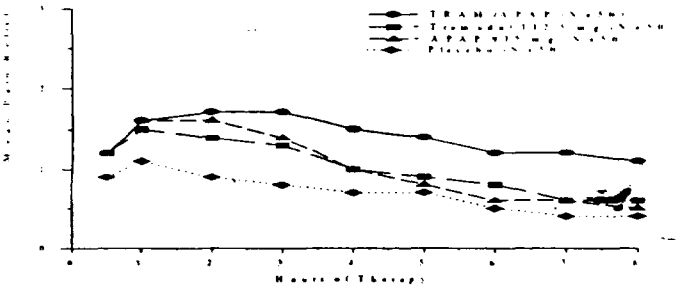
[a] Treatment means with a common letter (i.e., A,B,C,D) are not significantly different by Fisher's LSD at a level of 0.05. For each treatment group mean (SD), the number of subjects remaining in the trial is displayed at each time point.

[b] Statistically significant difference among all treatment groups at $p \leq 0.05$, F-test.

Pain intensity rating scale: 0=none; 1=mild; 2=moderate; 3=severe.

Data source: ANAG-004 report , Page 22

Figure C3: Mean Pain Relief (PAR) Scores Over Time (Extrapolated)
(All Randomized Subjects; Protocol TRAMAP-ANAG-005)



Pain relief rating scale: 0 = none; 1 = a little; 2 = some; 3 = a lot; 4 = complete

Table C5: Mean Pain Relief (PAR) Scores[a] Over Time (Extrapolated)
(All Randomized Subjects; Protocol TRAMAP-ANAG-005)

	Hours								
Treatment	0.50	1	2	3	4	5	6	7	8
TRAM/APAP	1.2 (1.13)	1.6 (1.30)	1.7 (1.38)	1.7 (1.41)	1.5 (1.43)	1.4 (1.44)	1.2 (1.42)	1.2 (1.40)	1.1 (1.46)
	A	A	A	A	A	A	A	A	A
	50	50	47	37	33	27	22	16	16
TRAM 112.5 mg	1.2 (0.95)	1.5 (1.09)	1.4 (1.25)	1.3 (1.44)	1.0 (1.47)	0.9 (1.45)	0.8 (1.39)	0.6 (1.23)	0.6 (1.16)
	A	AB	AB	AB	AB	AB	AB	B	B
	50	50	46	37	27	18	15	13	8
APAP 975 mg	1.2 (1.09)	1.6 (1.23)	1.6 (1.32)	1.4 (1.37)	1.0 (1.23)	0.8 (1.18)	0.6 (0.97)	0.6 (1.03)	0.5 (0.93)
	A	A	A	A	AB	B	B	B	B
	50	49	43	36	28	21	14	9	8
Placebo	0.9 (1.00)	1.1 (1.10)	0.9 (1.15)	0.8 (1.11)	0.7 (1.13)	0.7 (1.18)	0.5 (0.99)	0.4 (0.86)	0.4 (0.88)
	A	B	B	B	B	B	B	B	B
	50	48	45	25	20	14	13	10	7
P-Value[b]	0.516	0.081	0.020	0.007	0.033	0.049	0.024	0.011	0.007
RMS Error	1.045	1.181	1.277	1.339	1.323	1.320	1.211	1.150	1.132

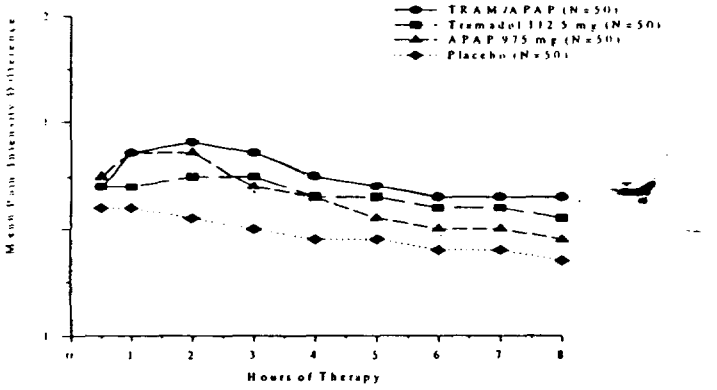
[a] Treatment means with a common letter (i.e., A,B,C) are not significantly different by Fisher's LSD at a level of 0.05. For each treatment group mean (SD), the number of subjects remaining in the trial is displayed at each timepoint.

[b] Statistically significant difference among all treatment groups at $p \leq 0.05$, F-test.

Pain relief scale: 0 = none; 1 = a little; 2 = some; 3 = a lot; 4 = complete.

Data source: ANAG-005 report , Page 22

Figure C4: Mean Pain Intensity Difference (PID) Scores Over Time (Extrapolated)
(All Randomized Subjects; Protocol TRAMAP-ANAG-005)



Pain intensity rating scale: 0 = none; 1 = mild; 2 = moderate; 3 = severe.

Table C6: Mean Pain Intensity Difference[a] (PID) Scores Over Time (Extrapolated)
(All Randomized Subjects; Protocol TRAMAP-ANAG-005)

	Hours								
Treatment	0.50	1	2	3	4	5	6	7	8
TRAM/APAP	0.4 (0.64)	0.7 (0.86)	0.8 (0.92)	0.7 (0.97)	0.5 (0.93)	0.4 (0.90)	0.3 (0.91)	0.3 (0.86)	0.3 (0.88)
	AB	A	A	A	A	A	A	A	A
	50	50	47	37	33	27	22	16	16
TRAM 112.5 mg	0.4 (0.61)	0.4 (0.73)	0.5 (0.76)	0.5 (0.89)	0.3 (0.87)	0.3 (0.86)	0.2 (0.80)	0.2 (0.71)	0.1 (0.69)
	AB	AB	A	A	A	A	AB	AB	AB
	50	50	46	37	27	18	15	13	8
APAP 975 mg	0.5 (0.71)	0.7 (0.88)	0.7 (0.96)	0.4 (0.86)	0.3 (0.83)	0.1 (0.78)	-0.0 (0.71)	-0.0 (0.71)	-0.1 (0.65)
	A	A	A	A	AB	AB	BC	BC	BC
	50	49	43	36	28	21	14	9	8
Placebo	0.2 (0.67)	0.2 (0.68)	0.1 (0.95)	-0.0 (0.89)	-0.1 (0.85)	-0.1 (0.89)	-0.2 (0.79)	-0.2 (0.69)	-0.3 (0.66)
	B	B	B	B	B	B	C	C	C
	50	48	45	25	20	14	13	10	7
P-Value[b]	0.123	0.001	0.003	0.001	0.009	0.034	0.011	0.004	0.002
RMS Error	0.657	0.793	0.899	0.904	0.872	0.860	0.807	0.745	0.728

[a] Treatment means with a common letter (i.e., A,B,C) are not significantly different by Fisher's LSD at a level of 0.05. For each treatment group mean (SD), the number of subjects remaining in the trial is displayed at each timepoint.

[b] Statistically significant difference among all treatment groups at $p \leq 0.05$, F-test.

Pain intensity rating scale: 0 = none; 1 = mild; 2 = moderate; 3 = severe.

Data source: ANAG-005 report , Page 23

Table C7: Selected Percentiles for Time (minutes) to Remedication
(Subjects Evaluable for Efficacy; Protocol TRAMAP-ANAG-004)

Treatment	N	25th	50th (Median)	75th
TRAM/APAP	51	--[a]	--[a]	--[a]
TRAM 112.5 mg	48	--[a]	--[a]	--[a]
APAP 975 mg	50	288.0	--[a]	--[a]
Placebo	50	135.0	245.0	--[a]

[a] Percentile not estimable.

Data source: ANAG-004 report , Page 27

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Appendix D

Data from Multiple-Dose Trials

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Appendix E

Safety Evaluation

16 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

DIVISION OF ANTI-INFLAMMATORY, ANALGESIC
AND OPHTHALMIC DRUG PRODUCTS

Medical Officer Review

NDA 21-123 – ULTRACET

Type of submission:	Complete response to Approvable letter.
Generic Name:	Tramadol 37.5 mg/APAP 325 mg
Pharmacological Class:	Centrally acting synthetic analgesic/NSAID.
Proposed Indications:	For the management of moderate to moderately severe acute pain.
Reviewer:	Maria Lourdes Villalba, M.D.
Date submitted:	November 14, 2000
Review completed:	May 11, 2001
Project Manager:	Yoon Kong
Related reviews:	Review of NDA 21-123, Correspondences dated June 22, 2000, June 28,2000, August 10, 2000 and September 15, 2000; NDA 20-281, ULTRAM (tramadol hydrochloride) original submission; NDA 20-281/s018; NDA 20-281 memo to file dated 4/26/01.

Cc: Division File/HFD 550
HFD 550/ MO/MLVillalba
HFD 550/ TL/LGoldkind
HFD 550/ PM/Ykong
HFD 550/ Biopharm/DBashaw
HFD 550/ Pharmtox/CChen

Maria Lourdes Villalba, M.D.

/S/

Lawrence Goldkind, M.D.
Team Leader, DAAODP

1. Background

On June 30, 2000, FDA issued an "Approvable" Action letter to NDA 21-123 (Ultracet) for acute pain, pending satisfactory resolution of the following clinical issues:

1. Further characterization of multiple-dose effects and dose-response relationships to support the dosing recommendations. (a. The effect of a single tablet dose in acute pain and b. Short-term multiple dose effect)
2. Clinical benefits of the combination tablets at the proposed dose over placebo in acute pain conditions other than the dental pain model.
3. Adequate safety information upon the dosing recommendation established for the treatment of acute pain.
4. Analyses of adverse events by age.

[redacted]

Reviewer's comment:

The current submission consists of the safety update and the revised labeling for ULTRACET for the short term management of acute pain. The deficiencies cited in the June Approvable letter have been addressed in the sponsor's correspondences dated June 22, June 28, August 10 and September 15, 2000. The sponsor's June and August's correspondences were submitted to the Agency as part of pre-meeting packages and have been addressed in my reviews dated July 21 and August 31, 2000.

In the future, data submitted as correspondence but intended to be part of a response to an action letter should be re-submitted with the complete response.

2. Summary of Responses to Deficiencies

Deficiency #1. Need for further characterization of acute dosing recommendations

a. Effect of a single tablet dose in acute pain

The sponsor proposes to use **two tablets** every 4 to 6 hours up to a maximum of 8 tablets a day instead of the original proposal of one to two tablets every 4 to 6 hours.

> *Reviewer's comment. The Division currently recommends that sponsors determine the minimum effective dose of analgesic products. However, the applicant's proposal is acceptable. If the applicant wishes to include the use of a single table dose in the label, additional efficacy data to support this dosing will be necessary. The use of a maximum dose of 8 tablets a day needs to be supported by the safety database (see below, deficiency #3).*

b. Lack of multiple dose study on acute pain.

The recommended dosing interval for ULTRACET is based upon PK of the components. Since there are no PK interactions, the recommended interval is based upon the tramadol component and follows the current ULTRAM label.

> *Reviewer's comment: The Division currently recommends short-term repeat dose studies to address optimal dosing interval. However, this requirement had not been specifically discussed during FDA-sponsor meetings prior to NDA submission. The applicant's rationale for the chosen dosing interval is acceptable.*

c. Additional issue: Support for acute pain, but not for acute **moderate** to **severe** pain.

Based on label of ULTRAM, the sponsor proposes labeling for treatment of moderate to severe pain. However, the 3 pivotal studies for ULTRACET were conducted in dental pain models, which used ibuprofen 400 mg as the active comparator and required a minimum VAS score of 5 out of 10 (moderate pain). Other recently approved analgesics that used the same pain model along with other surgical models (e.g. orthopedic surgery) have not receive the indication of moderate to severe pain, just acute pain.

Deficiency # 2: Need to provide efficacy data in a second acute pain model.

To establish efficacy of ULTRACET (two tablets) in a second pain model, the sponsor proposes to use data from NDA 20-281 (Ultram).

> *Reviewer's comment: The applicant's proposal to partially rely on original NDA 20-281 data is acceptable. Tramadol hydrochloride 75 mg was positive in two out of three studies in surgical pain models (gynecologic surgery and Cesarean section model) (The reader is referred to M.O. review, February 28, 1995).*

Deficiency # 3: Minimum safety requirements.

The sponsor proposes the use of a maximum of 8 tablets/day (300 mg of tramadol and 3,000 mg acetaminophen). The maximum daily doses of the components are lower than the maximum recommended doses of the individual products.

The safety assessment of analgesics must include adequate assessment based on ICH guidelines using maximum-labeled dose. In the case of combination products, the previous experience with comparable doses of each component may form part of the safety database. However, tramadol hydrochloride is an opioid product with potential for physical dependence and abuse, [redacted] Acetaminophen has a relatively narrow therapeutic index. Therefore, adequate safety assessment at maximum labeled dose is important.

Reviewer's comment: The Division's current safety requirement for short term management of pain is a safety database of 300 patients for 6 months and 100 patients for one year (ICH guidelines) at the maximum recommended dose, assuming that there is potential for using the product in the setting of [redacted]

By the time of NDA submission, a total of 156 patients received ζ8 tablets/day in the whole ULTRACET program, of whom 86 took it for 6 months or more. As per the applicant's Correspondence submitted June 22, 2000, ***310 subjects were exposed to the maximum dose of two tablets QID for 5 days.*** *Therefore, the use of ULTRACET should be limited to a maximum of 5 days, until additional safety data are provided.*

[redacted]

Of note, the table includes the run-in periods. It is unlikely that patients took high doses during the initial days of treatment. Additionally, these patients took one or two tablets up to 8 tablets a day, therefore, Table 1 does not reflect the safety of the dose that is being approved for acute pain: two tablets q 4-6 hours.

The sponsor will be requested to provide a table that more adequately reflects the safety of tramadol 75 mg and acetaminophen 650 mg to be included in the label.

Table 1: Cumulative Incidence of Most Common Adverse Events During Short-term treatment with ULTRACET.

	37.5 tramadol/325 acetaminophen (N=1,437)
Body System	
Preferred Term	%
Gastrointestinal System	
Nausea	15
Constipation	7
Vomiting	5
Dry Mouth	5
Dyspepsia	3
Diarrhea	2
Central & Peripheral Nervous System	
Dizziness	13
Headache	7
CNS Stimulation[b]	4
Psychiatric Disorders	
Somnolence	11
Insomnia	2
Skin and Appendages	
Pruritus	5
Sweating Increased	3
Body as a Whole	
Fatigue	4

[a] Preferred term reported by ≥2.0% of subjects during short term treatment with ULTRACET; estimates were obtained using the life table analysis.
[b] Composite of nervousness, anxiety, agitation, euphoria, emotional lability and hallucinations (coded under psychiatric disorders) and hypertonia and tremor (coded under CNS disorders).
Source: Modified from sponsor's proposed table of AE in the ULTRACET label.

Deficiency #4: Age analysis

Of 1,437 patients exposed in [redacted] studies, 505 patients were elderly. To address deficiency #4, the applicant has provided summaries of adverse events summarized by age in long term pain trials (June 22, 2000, appendix H). The sponsor states that no significant differences in adverse event profile were found between elderly and younger than 65 years of age.

4.1 Elderly exposure in acute pain

Ultracet is being approved for the acute pain indication, however, the range of patients in the dental pain studies was 16 to 53 years. Therefore, there are no data on the use of two tablets a single dose in the elderly.

Reviewer's comments: The acute surgical pain studies included patients with an age range of 18 to 83, of whom 101 received a single dose of 3 ULTRACET tablets. The sponsor has been requested to provide number of elderly patients who may have received three tablets at once in the surgical pain studies. This information is outstanding.

[redacted]

To evaluate exposure in elderly patients during the first five days of treatment, this M.O. requested the sponsor to provided the number of elderly patients who took 8,7,6 and 5 tablets a day for5 days. This information is outstanding.

Table 2 presents the incidence of dropouts due to adverse events by body system and by age during the first five days of treatment.

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Table 2. Dropouts due to AE's (incidence of ζ0.4%) in patients exposed to Ultracet for the first five days by age and body system (total = 1,437)

Body system	< 65 years N= 932 (%)	≥65 years N= 505
# patients who discontinued due to any AE	57 (6.1)	42 (8.3)
GI disorder	**32 (3.4)**	**27 (5.3)**
Nausea	25 (2.7)	23 (4.6)
Vomiting	12 (1.3)	3 (0.6)
Constipation	2 (0.2)	4 (0.8)
C&Periph Nervous System	**32 (3.4)**	**21 (4.2)**
Dizziness	19 (2.0)	14 (2.8)
Headache	11 (1.2)	8 (1.6)
Psychiatric	**11 (1.2)**	**15 (3.0)**
Somnolence	4 (0.4)	12 (2.4)
Body as a whole	**11 (1.2)**	**5 (1.0)**
Fatigue/asthenia	5 (0.5)	4 (0.8)
Skin and appendages	**9 (1.0)**	**6 (1.2)**
Pruritus	6 (0.6)	4 (0.8)
Urinary system disorders	**2 (0.2)**	**3 (0.6)**
Micturition disorder	0 (0.0)	2 (0.4)

Source: Provided 4/27/01 at the reviewer's request. Numbers include patients discontinued due to adverse events during the run-in period.

> *Reviewer's comment: Despite the fact that patients were taking one or two tablets q 4-6 hours and that some studies had a run-in period (therefore patients were probably not taking high doses of ULTRACET), there is a trend towards a higher incidence of discontinuations due to adverse events in the elderly group.* ***Discontinuations due to somnolence within the first 5 days of treatment was six-fold higher in the elderly (2.4%) as compared to non-elderly patients (0.4%).***

4.3 Elderly exposure to tramadol alone in NDA -281.

Review of data from the original NDA 20-281 provides valuable information regarding exposure to tramadol alone in elderly patients.

Table 3. Average daily dosage (mg) of ULTRAM by visit for subjects <65 and ζ65 years of age in double blind phase of long term multiple dose studies (protocols TKM TKB and TL2.

Visit week	Protocol TKM[1]				Protocols TKB[2] and TL2[3]			
	<65 years		ζ65 years		<65 years		ζ65 years	
	N	mean (SD)	N	mean (SD)	N	mean (SD)	N	mean (SD)
1	36	221 (16.0)	44	227 (13.6)	131	235 (8.7)	246	214 (5.9)
2	23	226 (23.5)	33	235 (19.3)	106	256 (9.9)	199	241 (6.9)
5	-		-		91	272 (10.7)	24	200 (19.3)
9	-		-		76	282 (11.6)	18	180 (23.3)
Final visit	36	219 (17.1)	43	235 (15.5)	128	278 (9.0)	243	236 (6.3)

[1] TKM was a 4-week study in malignant pain. [2,3] TKB and TL2 were non-malignant [redacted] studies in low back pain and osteoarthritis. Source: Sponsor's Table 13. ISS, SLR 019.

Reviewer's comment:

As seen in Table 3, the amount of tramadol taken by patients during the three-month non-malignant pain studies (TKB and TL2) was consistently lower among elderly patients. This difference increased as the trials progressed. By week 9, the average dosage of ULTRAM was 282 mg/day and 180 mg/day, for the <65 and ζ65 years respectively (a difference in means of two tablets between elderly and non-elderly). Of note, TKB (12-week study) included 12 elderly patients. Of 234 patients enrolled in TL2 (4-week study in elderly), 70% (163 patients) completed the double blind phase. Of those, 140 continued the open label phase. However, by week 9 only 18 (7%) elderly patients remained from the two studies, compared to 76 (58%) of the non-elderly patients. Therefore, the percentage of patients who discontinued from the non-malignant pain studies was twice among the elderly as compared to the <65 year old patients (93% and 42%, respectively).

The wide dose range allowed in the [redacted] studies (one or two tablets every 4 to 6 hours) and the self adjustment of dosing according to tolerance, obscured potential differences in safety between elderly and non-elderly. Therefore it is not possible to adequately compare overall safety between the elderly and non-elderly.

4.4 Conclusions regarding safety in the elderly:

- 505 elderly patients were included in the multiple dose studies with ULTRACET.
- There is no available information regarding the average and maximum dose of ULTRACET received by elderly patients during these studies.
- Review of data from tramadol alone indicates that elderly patients took lower doses of tramadol than their non-elderly counterparts (180 mg vs 281 mg, respectively, at week 9).
- ULTRAM limits the use of tramadol in the older –elderly to a maximum of 300 mg/day. The maximum dose of tramadol used as part of the ULTRACET tablet would be 300 mg.
- It is not possible to adequately compare overall safety of ULTRACET between the elderly and non-elderly. There are no adequate data to provide dosage guidance in the elderly.
- A generic precautionary statement should be included in the label for use in the elderly.

3. Safety Update

[redacted]

4. Conclusions: Two tablets of ULTRACET have demonstrated evidence of efficacy for the short term management of acute pain. The safety database supports the use of up to 8 tablets a day for five days. Safety data in elderly patients are limited.

5. Recommendation for Regulatory Action: Approvable for the treatment of acute pain.

Additional recommendations:

1. FDA Proposed label is presented in Attachment 1.

Major differences between FDA and applicant's proposed label are:

- Ultracet labeling includes changes requested for the ULTRAM (NDA 20-281) updated label, sent to [redacted] RWJ in May 2001.
- The indication is the short-term (five days or less) management acute pain.

- Under Clinical Study Section, Single Dose studies, description of the analgesic effect of ULTRACET has been modified. A graph representing pain relief in one of the acute pain studies is included in the label.
- Potential for liver toxicity due to the acetaminophen component of ULTRACET has been strengthened throughout the label.

2. The applicant should follow current Center recommendations for the format of the Toxicology section of the label. When animal data is mentioned, all doses should be changed to mg/m^2 and dose ratios of animal dose to the human dose should be calculated.

3. The applicant should provide a table of adverse events that more adequately reflects the safety of short term treatment with tramadol 75 mg and acetaminophen 650 mg.

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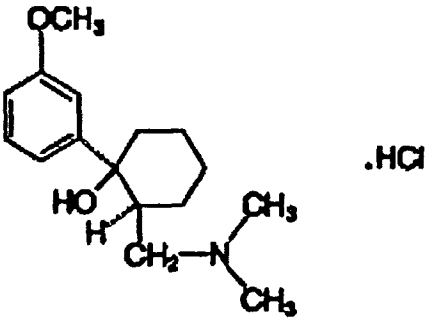
Attachment 1

ULTRACET (tramadol hydrochloride/ acetaminophen tablets)

DESCRIPTION

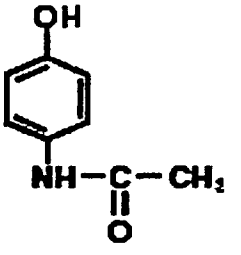
ULTRACET™ (37.5 mg tramadol hydrochloride/ 325 mg acetaminophen tablets) combines two analgesics, tramadol and acetaminophen.

The chemical name for tramadol hydrochloride is (±)cis-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride. Its structural formula is:



The molecular weight of tramadol hydrochloride is 299.84. Tramadol hydrochloride is a white, bitter, crystalline and odorless powder.

The chemical name for acetaminophen is N-acetyl-p-aminophenol. It's structural formula is:



The molecular weight of acetaminophen is 151.17. Acetaminophen is an analgesic and antipyretic agent which occurs as a white, odorless, crystalline powder, possessing a slightly bitter taste.

ULTRACET Tablets contain 37.5 mg tramadol hydrochloride and 325 mg acetaminophen and are light yellow in color. Inactive ingredients in the tablet are powdered cellulose, pregelatinized starch, sodium starch glycolate, starch, purified water, magnesium stearate, OPADRY® Light Yellow, and carnauba wax.

CLINICAL PHARMACOLOGY

The following information is based on studies of tramadol alone or acetaminophen alone, except where otherwise noted:

Pharmacodynamics

Tramadol is a centrally acting synthetic opioid analgesic [redacted] Although its mode of action is not completely understood, from animal tests, at least two complementary mechanisms appear applicable: binding of parent and M1 metabolite to μ-opioid receptors and weak inhibition of reuptake of norepinephrine and serotonin.(blank space)

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 opiate 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, Pharmacokinetics).

Tramadol has been shown to inhibit reuptake of norepinephrine and serotonin in vitro, as have some other opioid analgesics. These mechanisms may contribute independently to the overall analgesic profile of tramadol.

Apart from analgesia, tramadol administration may produce a constellation of symptoms (including dizziness, somnolence, nausea, constipation, sweating and pruritus) similar to that of other opioids.

Acetaminophen

Acetaminophen is a non-opiate, non-salicylate analgesic.

Pharmacokinetics

Tramadol is administered as a racemate and both the [-] and [+] forms of both tramadol and M1 are detected in the circulation. The pharmacokinetics of plasma tramadol and acetaminophen following oral administration of one ULTRACET tablet are shown in Table 1. Tramadol has a slower absorption and longer half-life, when compared to acetaminophen.

Table 1: Summary of Mean (±SD) Pharmacokinetic Parameters of the (+)- and (-) Enantiomers of Tramadol and M1 and Acetaminophen Following A Single Oral Dose Of One Tramadol/Acetaminophen Combination Tablet (37.5 mg/325 mg) in Volunteers

Parameter[a]	(+)-Tramadol		(-)-Tramadol		(+)-M1		(-)-M1		acetaminophen	
C_{max} (ng/mL)	64.3	(9.3)	55.5	(8.1)	10.9	(5.7)	12.8	(4.2)	4.2	(0.8)
t_{max} (h)	1.8	(0.6)	1.8	(0.7)	2.1	(0.7)	2.2	(0.7)	0.9	(0.7)
CL/F (mL/min)	588	(226)	736	(244)	-	-	-	-	365	(84)
$t_{1/2}$ (h)	5.1	(1.4)	4.7	(1.2)	7.8	(3.0)	6.2	(1.6)	2.5	(0.6)

[a] For acetaminophen, C_{max} was measured as µg/mL.

A single dose pharmacokinetic study of ULTRACET in volunteers showed no drug interactions between tramadol and acetaminophen. Upon multiple oral dosing to steady state, however, the bioavailability of tramadol and metabolite M1 was lower for the combination tablets compared to tramadol administered alone. The [redacted] decrease [redacted] in AUC were 14.0% for (+)-tramadol and 24.2% for (-)-M1. The cause of this reduced bioavailability is not clear. Following single or multiple dose administration of Ultracet, no significant change in acetaminophen pharmacokinetics was observed when compared to acetaminophen given alone.

Absorption:

The absolute bioavailability of tramadol from ULTRACET tablets has not been determined. Tramadol hydrochloride has a mean absolute bioavailability of approximately 70% following administration of a single 100 mg oral dose of ULTRAM® tablets. The mean peak plasma concentration of racemic tramadol and M1 after administration of two ULTRACET tablets occur at approximately three hours post-dose. Oral absorption of acetaminophen following administration of ULTRACET [redacted] occurs primarily in the small intestine. Peak plasma concentrations of acetaminophen occur within one hour and are not affected by co-administration with tramadol.

Food Effects: When ULTRACET was administered with food, the time to peak plasma concentration was delayed for approximately 35 minutes for tramadol and almost one hour for acetaminophen. However, peak plasma concentration or the extent of absorption of either tramadol or acetaminophen were not affected.

Distribution:

The volume of distribution of tramadol was 2.6 and 2.9 L/kg in male and female subjects, respectively, following a 100 mg intravenous dose. The binding of tramadol to human plasma proteins is approximately 20% and binding also appears to be independent of concentration up to 10 µg/mL. Saturation of plasma protein binding occurs only at concentrations outside the clinically relevant range.

Acetaminophen appears to be widely distributed throughout most body tissues except fat. Its apparent volume of distribution is about 0.9 L/kg. A relative small portion (~20%) of acetaminophen is bound to plasma protein.

Metabolism:

Following oral administration, tramadol is extensively metabolized by a number of pathways, including CYP2D6 and CYP3A4, as well as by conjugation of parent and metabolites. Approximately 30% of the dose is excreted in the urine as unchanged drug, whereas 60% of the dose is excreted as metabolites. The major metabolic pathways appear to be *N*- and *O*- demethylation and glucuronidation or sulfation in the liver. Metabolite M1 (*O*-desmethyltramadol) is pharmacologically active in animal models. [redacted] of M1 is dependent on [redacted] and as such is subject to [redacted] inhibition which may affect the therapeutic response.

Approximately 7% of the population has reduced activity of the CYP2D6 isoenzyme of cytochrome P450. These individuals are "poor metabolizers" of debrisoquine, dextromethorphan, tricyclic antidepressants, among other drugs. Based on a population PK analysis of Phase 1 studies in healthy subjects, concentrations of tramadol were approximately 20% higher in "poor metabolizers" versus "extensive metabolizers", while M1 concentrations were 40% lower. In vitro drug interaction studies in human liver microsomes indicates that inhibitors of CYP2D6 such as fluoxetine and its metabolite norfluoxetine, amitriptyline and quinidine inhibit the metabolism of tramadol to various degrees. The full pharmacological impact of these alterations in terms of either efficacy or safety is unknown. Concomitant use of SEROTONIN re-uptake INHIBITORS and MAO INHIBITIORS may enhance the risk of adverse events, including seizure(see WARNINGS) and serotonin syndrome.

Acetaminophen is primarily metabolized in the liver by first-order kinetics and involves three principle separate pathways:

a) conjugation with glucuronide;

b) conjugation with sulfate; and

c) oxidation via the cytochrome, P450-dependent, mixed-function oxidase enzyme pathway to form a reactive intermediate metabolite, which conjugates with glutathione

and is then further metabolized to form cysteine and mercapturic acid conjugates. The principal cytochrome P450 isoenzyme involved appears to be CYP2E1, with CYP1A2 and CYP3A4 as additional pathways.

In adults, the majority of acetaminophen is conjugated with glucuronic acid and, to a lesser extent, with sulfate. These glucuronide-, sulfate-, and glutathione-derived metabolites lack biologic activity. In premature infants, newborns, and young infants, the sulfate conjugate predominates.

Elimination

Tramadol is eliminated primarily through metabolism by the liver and the metabolites are eliminated primarily by the kidney. The plasma elimination half-lives of racemic tramadol and M1 are approximately 5-6 and 7 hours, respectively. The apparent plasma elimination half-life of racemic tramadol increased to 7-9 hours upon multiple dosing. The half-life of acetaminophen is about 2 to 3 hours in adults. It is somewhat shorter in children and somewhat longer in neonates and in cirrhotic patients. Acetaminophen is eliminated from the body primarily by formation of glucuronide and sulfate conjugates in a dose-dependent manner. Less than 9% of acetaminophen is excreted unchanged in the urine.

Special Populations

Renal:

The pharmacokinetics of [redacted] in patients with renal impairment have not been studied. Based on studies using tramadol alone, excretion of tramadol and metabolite M1 is reduced in patients with creatinine clearance of less than 30 mL/min, adjustment of dosing regimen in this patient population is recommended. (See DOSAGE AND ADMINISTRATION). The total amount of tramadol and M1 removed during a 4-hour dialysis period is less than 7% of the administered dose based on studies using tramadol alone.

Hepatic:

The pharmacokinetics and tolerability of ULTRACET in patients with impaired hepatic function has not been studied. Since tramadol and acetaminophen are both extensively metabolized by the [redacted] the use of ULTRACET in patients with hepatic impairment is not recommended (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

A population pharmacokinetic analysis of data obtained from a clinical trial in patients with chronic pain treated with ULTRACET which included 55 patients between 65 and 75 years of age and 19 patients over 75 years of age, showed no significant changes in pharmacokinetics of tramadol and acetaminophen in elderly patients with normal renal and hepatic function. (See PRECAUTIONS: Geriatric Use)

Gender:

Tramadol clearance was 20% higher in female subjects compared to males on four phase I studies of ULTRACET in 50 male and 34 female healthy subjects. The clinical significance of this difference is unknown.

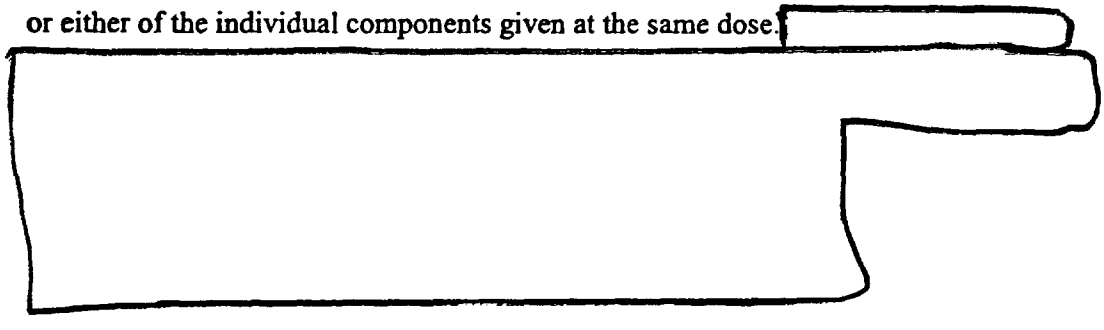
Pediatric:

Pharmacokinetics of ULTRACET Tablets have not been studied in pediatric patients below 16 years of age.

Clinical Studies

Single Dose Studies for Treatment of Acute Pain

In pivotal single-dose studies in acute pain, two tablets of ULTRACET administered to patients with pain following oral surgical procedures provided greater relief than placebo or either of the individual components given at the same dose.



INDICATIONS AND USAGE

ULTRACET is indicated for the short-term (five days or less) management of acute pain.

CONTRAINDICATIONS

ULTRACET should not be administered to patients who have previously demonstrated hypersensitivity to tramadol, acetaminophen, any other component of this product or opioids.

ULTRACET is contraindicated in any situation where opioids are contraindicated, including acute intoxication with alcohol, hypnotics, narcotics, centrally acting analgesics, opioids or psychotropic drugs. ULTRACET may worsen central nervous system and respiratory depression in these patients.

WARNINGS

Seizure Risk

Seizures have been reported in patients receiving tramadol within the recommended dosage range. Spontaneous post-marketing reports indicate that seizure risk is increased with doses of tramadol above the recommended range. Concomitant use of tramadol increases the seizure risk in patients taking:

- **Selective serotonin reuptake inhibitors (SSRI antidepressants or anorectics),**
- **Tricyclic antidepressants (TCAs), and other tricyclic compounds (e.g., cyclobenzaprine, promethazine, etc.), or**
- **Opioids.**

Administration of tramadol may enhance the seizure risk in patients taking:

- **MAO inhibitors (see also WARNINGS - Use with MAO Inhibitors),**
- **Neuroleptics, or**
- **Other drugs that reduce the seizure threshold.**

Risk of convulsions may also increase in patients with epilepsy, those with a history of seizures, or in patients with a recognized risk for seizure (such as head trauma, metabolic disorders, alcohol and drug withdrawal, CNS infections). In tramadol overdose, naloxone administration may increase the risk of seizure.

Anaphylactoid Reactions

Serious and rarely fatal anaphylactoid reactions have been reported in patients receiving therapy with tramadol. When these events do occur it is often following the first dose. Other reported reactions include pruritus, hives, bronchospasm, angioedema, toxic epidermolitic necrolysis and Steven Johnson. Patients with a history of anaphylactoid reactions to codeine and other opioids may be at increased risk and therefore should not receive ULTRACET (see CONTRAINDICATIONS).

Respiratory Depression

Administer ULTRACET cautiously in patients at risk for respiratory depression. When large doses of tramadol are administered with anesthetic medications or alcohol, respiratory depression may result. Respiratory depression should be treated as an overdose. If naloxone is to be administered, use cautiously because it may precipitate seizures (see WARNINGS , Seizure Risk and OVERDOSAGE).

Increased Intracranial Pressure or Head Trauma

The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, and may be markedly exaggerated in the presence of head injury, intracranial lesions or other sources of preexisting increased intracranial pressure. ULTRACET should be used with caution in these patients. Pupillary changes (miosis) from tramadol may obscure the existence, extent, or course of intracranial pathology. Clinicians should also maintain a high index of suspicion for adverse drug reaction when evaluating altered mental status in these patients if they are receiving ULTRACET.

[redacted]

Use with MAO inhibitors and Serotonin re-uptake inhibitors

Use ULTRACET with great caution in patients taking monoamine oxidase inhibitors. [redacted] Animal studies have shown increased deaths with combined administration of MAO inhibitors and tramadol. Concomitant use of [redacted] with MAO inhibitors or SSRI's increases the risk of adverse events, including seizure and serotonin syndrome.

Use with Alcohol

Chronic alcohol use increases the risk of acetaminophen liver toxicity. ULTRACET should not be used concomitantly with alcohol consumption. The use of ULTRACET in patients with liver disease [redacted] is not recommended.

Use with other acetaminophen-containing products

[redacted]

Withdrawal

Withdrawal symptoms may occur if [redacted] is discontinued abruptly. These symptoms may include: anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhea, upper respiratory symptoms, piloerection, and rarely hallucinations. Clinical experience suggests that withdrawal symptoms may be relieved by tapering the medication. (See DRUG ABUSE AND DEPENDENCE).

Physical Dependence and Abuse

Tramadol may induce psychic and physical dependence of the morphine-type (μ-opioid). Tramadol should not be used in opioid-dependent patients. [redacted] has been shown to reinitiate physical dependence in some patients that have been previously dependent on other opioids. Drug dependence and abuse, including drug-seeking behavior and taking illicit actions to obtain the drug are not limited to those patients with prior history of opioid dependence. (See DRUG ABUSE AND DEPENDENCE).

Risk of Overdosage.

Serious potential consequences of overdosage with tramadol are central nervous system depression, respiratory depression and death. In treating an overdose, primary attention should be given to maintaining adequate ventilation along with general supportive treatment [redacted] (See OVERDOSAGE).

PRECAUTIONS

General

The recommended dose of ULTRACET should not be exceeded.

Do not co-administer ULTRACET with other tramadol [redacted] or acetaminophen-containing products [redacted]

Pediatric Use

The safety and effectiveness of ULTRACET has not been studied in the pediatric population.

Geriatric Use

In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function; of concomitant disease and multiple drug therapy.

Acute Abdominal Conditions

The administration of ULTRACET may complicate the clinical assessment of patients with acute abdominal conditions.

Use in Renal Disease

ULTRACET has not been studied in patients with impaired renal function. Experience with tramadol suggest that impaired renal function results in a decreased rate and extent of excretion of tramadol and its active metabolite, M1. In patients with creatinine

clearances of less than 30 mL/min, it is recommended that the dosing interval of ULTRACET be increased not to exceed 2 tablets every 12 hours.

Use in Hepatic Disease

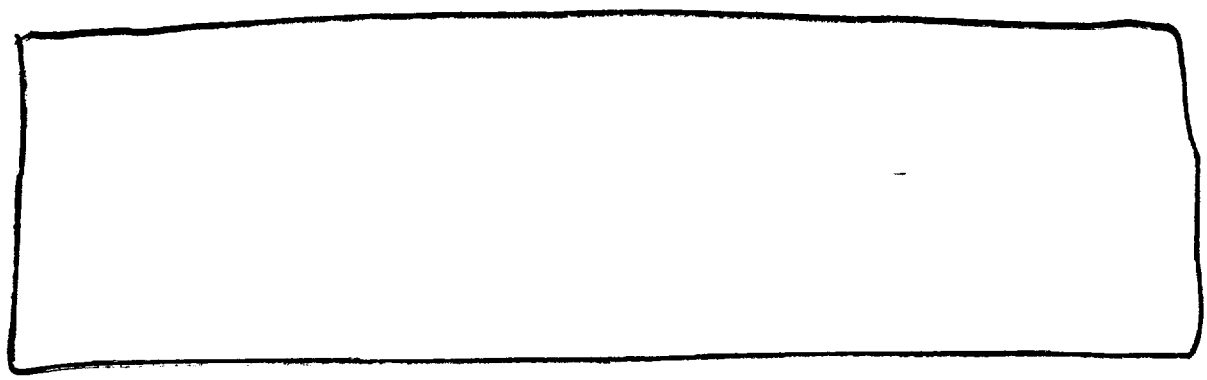
ULTRACET has not been studied in patients with impaired hepatic function. The use of ULTRACET in patients with hepatic impairment is not recommended (See WARNINGS, Use with alcohol)

Information for Patients

- ULTRACET may impair mental or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.
- ULTRACET should not be taken with alcohol containing beverages.
- The patient should be instructed not to take ULTRACET in combination with other tramadol or acetaminophen-containing products, including over-the-counter preparations.
- ULTRACET should be used with caution when taking medications such as tranquilizers, hypnotics or other opiate containing analgesics.
- The patient should be instructed to inform the physician if they are pregnant, think they might become pregnant, or are trying to become pregnant (see PRECAUTIONS: Labor and Delivery).
- The patient should understand the single-dose and 24-hour dose limit and the time interval between doses, since exceeding these recommendations can result in respiratory depression, seizures, hepatic toxicity and death.

Drug Interactions

In vitro studies indicate that tramadol is unlikely to inhibit the CYP3A4-mediated metabolism of other drugs when tramadol is administered concomitantly at therapeutic doses. Tramadol does not appear to induce its own metabolism in humans, since observed maximal plasma concentrations after multiple oral doses are higher than expected based on single-dose data. Tramadol is a mild inducer of selected drug metabolism pathways measured in animals.



Use with Quinidine

Tramadol is metabolized to M1 by the CYP2D6 [redacted] Quinidine is a selective inhibitor of that isoenzyme; so that concomitant administration of quinidine and tramadol results in increased concentrations of tramadol and reduced concentrations of M1. The clinical consequences of these findings are unknown. In vitro drug interaction studies in human liver microsomes indicate that tramadol has no effect on quinidine metabolism.

Use with Inhibitors of CYP2D6

In vitro drug interaction studies in human liver microsomes indicate that concomitant administration with inhibitors of CYP2D6 such as fluoxetine, paroxetine, and amitriptyline could result in some inhibition of the metabolism of tramadol.

Use with Cimetidine

Concomitant administration of ULTRACET and cimetidine has not been studied. Concomitant administration of tramadol and cimetidine does not result in clinically significant changes in tramadol pharmacokinetics.

Use with MAO Inhibitors

Interactions with MAO Inhibitors, due to interference with detoxification mechanisms, have been reported for some centrally acting drugs (see WARNINGS, Use with MAO Inhibitors).

Use with Digoxin

Post-marketing surveillance of tramadol has revealed rare reports of digoxin toxicity.

Use with Warfarin Like Compounds

Post-marketing surveillance of both tramadol and acetaminophen individual products have revealed rare alterations of warfarin effect, including elevation of prothrombin times.

While such changes have been generally of limited clinical significance for the individual products, periodic evaluation of prothrombin time should be performed when ULTRACET and warfarin-like compounds are administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility

There are no animal or laboratory studies on the combination product (tramadol and acetaminophen) to evaluate carcinogenesis, mutagenesis, or impairment of fertility.

A slight but statistically significant increase in two common murine tumors, pulmonary and hepatic, was observed in a mouse carcinogenicity study, particularly in aged mice [redacted]

Tramadol was not mutagenic in the following assays: Ames Salmonella microsomal activation test, CHO/HPRT mammalian cell assay, mouse lymphoma assay (in the absence of metabolic activation), dominant lethal mutation tests in mice, chromosome aberration test in Chinese hamsters, and bone marrow micronucleus tests in mice and Chinese hamsters. Weakly mutagenic results occurred in the presence of metabolic activation in the mouse lymphoma assay and micronucleus test in rats. Overall, the weight of evidence from these tests indicates that tramadol does not pose a genotoxic risk to humans.

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

Pregnancy

Teratogenic Effects: *Pregnancy Category C*

No drug-related teratogenic effects were observed in the progeny of rats treated orally with tramadol and acetaminophen. The tramadol/ acetaminophen combination product was shown to be embryotoxic and fetotoxic in rats at a maternally toxic dose (50/434 mg/kg tramadol/acetaminophen) times the maximum dose but was not teratogenic at this dose level. Embryo and fetal toxicity consisted of decreased fetal weights and increased supernumerary ribs

Non-teratogenic effects:
Tramadol alone was evaluated in peri- and post-natal studies in rats. Progeny of dams receiving oral (gavage) dose levels of 50 mg/kg or greater had decreased weights, and pup survival was decreased early in lactation at 80 mg/kg (the maximum human dose

There are no adequate and well-controlled studies in pregnant women. ULTRACET should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Neonatal seizures, neonatal withdrawal syndrome, fetal death and stillbirth have been reported with tramadol hydrochloride during post-marketing.

Labor and Delivery

ULTRACET should not be used in pregnant women prior to or during labor unless the potential benefits outweigh the risks. Safe use in pregnancy has not been established. Chronic use during pregnancy may lead to physical dependence and post-partum

withdrawal symptoms in the newborn. Tramadol has been shown to cross the placenta. The mean ratio of serum tramadol in the umbilical veins compared to maternal veins was 0.83 for 40 women given tramadol during labor.

The effect of ULTRACET, if any, on the later growth, development, and functional maturation of the child is unknown.

Nursing Mothers

ULTRACET is not recommended for obstetrical preoperative medication or for post-delivery analgesia in nursing mothers because its safety in infants and newborns has not been studied.

Following a single IV 100 mg dose of tramadol, the cumulative excretion in breast milk within 16 hours post-dose was 100 µg of tramadol (0.1% of the maternal dose) and 27 µg of M1.

ADVERSE REACTIONS

Table 2 reports the [redacted] incidence rate of [redacted] treatment-

[redacted]

APPEARS THIS WAY
ON ORIGINAL

[redacted]

ULTRACET

Body System Preferred Term	%
Gastrointestinal System	
Nausea	
Constipation	
[redacted]	
Diarrhea	
Central & Peripheral Nervous System	
Dizziness	
[redacted]	
Psychiatric Disorders	
Somnolence	
Insomnia	
Skin and Appendages	
Pruritus	
Sweating Increased	
[redacted]	

[redacted]

Incidence at least 1%, causal relationship at least possible or greater: the following lists adverse reactions that occurred with an incidence of at least 1% in single dose or repeated dose clinical trials of ULTRACET.

Body as a Whole – Asthenia, fatigue, hot flushes
Central and Peripheral Nervous System – Dizziness, headache, tremor
Gastrointestinal System – Abdominal pain, constipation, diarrhea, dyspepsia, flatulence, dry mouth, nausea, vomiting

Psychiatric Disorders – Anorexia, anxiety, confusion, euphoria, insomnia, nervousness, somnolence

Skin and Appendages – Pruritus, rash, increased sweating.

Selected Adverse events occurring at less than 1%: the following lists clinically relevant adverse reactions that occurred with an incidence of less than 1% in ULTRACET clinical trials:

Body as a Whole – Chest pain, rigors, syncope, withdrawal syndrome
Cardiovascular Disorders – Hypertension, aggravated hypertension, hypotension
Central and Peripheral Nervous System – Ataxia, convulsions, hypertonia, migraine, aggravated migraine, involuntary muscle contractions, paraesthesia, stupor, vertigo
Gastrointestinal System – Dysphagia, melena, tongue edema
Hearing and Vestibular Disorders – Tinnitus
Heart Rate and Rhythm Disorders – Arrhythmia, palpitation, tachycardia
Liver and Biliary System – Hepatic function abnormal
Metabolic and Nutritional Disorders – Weight decrease
Psychiatric Disorders – Amnesia, depersonalization, depression, drug abuse, emotional lability, hallucination, impotence, paranoia, abnormal thinking
Red Blood Cell Disorders – Anemia
Respiratory System – Dyspnea
Urinary System – Albuminuria, micturition disorder, oliguria, urinary retention
Vision Disorders – Abnormal vision

Other clinically significant adverse experiences previously reported with tramadol hydrochloride:

Other events which have been reported with the use of tramadol products and for which a causal association has not been determined include: vasodilation, orthostatic hypotension, myocardial ischemia, pulmonary edema, allergic reactions (including anaphylaxis and urticaria, Stevens Johnson Syndrome/TENS), cognitive dysfunction, difficulty concentrating, depression, suicidal tendency, hepatitis, liver failure and gastrointestinal bleeding. Reported laboratory abnormalities included elevated creatinine and liver function tests. Serotonin syndrome (whose symptoms may include mental status change, hyperreflexia, fever, shivering, tremor, agitation, diaphoresis, seizures and coma) has been reported with tramadol when used concomitantly with other serotonergic agents such as SSRIs and MAOIs.

Other clinically significant adverse experiences previously reported with acetaminophen. Allergic reactions (primarily skin rash) or reports of hypersensitivity secondary to acetaminophen are rare and generally controlled by discontinuation of the drug and, when

necessary, symptomatic treatment.

DRUG ABUSE AND DEPENDENCE

ULTRAM may induce psychic and physical dependence of the morphine-type □m-opioid)(See WARNING). Dependence and abuse, including drug-seeking behavior and taking illicit actions to obtain the drug are not limited to those patients with prior history of opioid dependence.

Withdrawal symptoms may occur if is discontinued abruptly. These symptoms may include: anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhea, upper respiratory symptoms, piloerection, and rarely hallucinations. Clinical experience suggests that withdrawal symptoms may be relieved by reinstitution of opioid therapy followed by a gradual, tapered dose reduction of the medication combined with symptomatic support.

OVERDOSAGE

ULTRACET is a combination product. The clinical presentation of overdose may include the signs and symptoms of tramadol toxicity, acetaminophen toxicity or both. The initial symptoms of tramadol overdosage may include respiratory depression and or seizures. The initial symptoms seen within the first 24 hours following an acetaminophen overdose are: anorexia, nausea, vomiting, malaise, pallor and diaphoresis.

Tramadol

Serious potential consequences of overdosage are respiratory depression, lethargy, coma seizure, cardiac arrest and death. (See WARNING). Fatalities have been reported in post marketing in association with both intentional and unintentional overdose with tramadol.

Acetaminophen

Renal tubular necrosis may also occur.

Treatment of overdose

A single or multiple overdose with ULTRACET potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended.

In treating an overdose of ULTRACET, primary attention should be given to maintaining adequate ventilation along with general supportive treatment. While naloxone will reverse some, but not all, symptoms caused by overdosage with tramadol, the risk of seizures is also increased with naloxone administration. In animals, convulsions following the administration of toxic doses of tramadol could be suppressed with barbiturates or benzodiazepines but were increased with naloxone. Naloxone administration did not change the lethality of an overdose in mice. Based on experience with tramadol, hemodialysis is not expected to be helpful in an overdose because it removes less than 7% of the administered dose in a 4-hour dialysis period.

Standard recommendations should be followed for the treatment of acetaminophen overdose.

DOSAGE AND ADMINISTRATION

For the short-term (5 days or less) management of acute pain, the recommended dose of ULTRACET is 2 tablets every 4 to 6 hours as needed for pain relief up to a maximum of 8 tablets per day.

Individualization of Dose

In patients with creatinine clearances of less than 30 mL/min, it is recommended that the dosing interval of ULTRACET be increased not to exceed 2 tablets every 12 hours. Dose selection for an elderly patient should be cautious, in view of the potential for greater sensitivity to adverse events.

HOW SUPPLIED

ULTRACET (37.5 mg tramadol hydrochloride/ 325 mg acetaminophen) Tablets (light yellow, film-coated capsule-shaped tablet) debossed "O-M" on one side and "650" on the other are available as follows:

20's: NDC 0045 0650 50 (Bottles of 20 tablets)

100's: NDC 0045 0650 60 (Bottles of 100 tablets).

500's: NDC 0045 0650 70 (Bottles of 500 tablets).

HUD 100's: NDC 0045 0650 10 (Packages of 100 unit doses in blister packs, 10 cards of 10 tablets each).

Dispense in a tight container. Store at 25°C (77°F); excursions permitted to 15 – 30°C (59 - 86°F).

DIVISION OF ANALGESIC, ANTIINFLAMMATORY AND OPHTHALMIC DRUG PRODUCTS (HFD-550)

Medical Officer Review

NDA 21-123

ULTRACET

(Tramadol hydrochloride 75 mg/acetaminophen 325 mg)

Type of submission:	Complete Response to Approvable letter
Sponsor:	RWJ
Indication:	For the short term management of acute pain
Date of submission:	June 14, 2001
Date of review:	August 15, 2001
PM:	M.J. Walling/ B.Gould
Reviewer:	Maria Lourdes Villalba, M.D.

1) Background

In response to the May 15, 2001 Approvable letter to NDA 21-123 (ULTRACET, tramadol hydrochloride 75 mg/acetaminophen 325 mg), RWJ submitted a Complete Response in June 14, 2001. Labeling of the tramadol component of ULTRACET is based on the ULTRAM label (NDA 20-281). Parallel negotiations were conducted for labeling changes to the ULTRAM label (NDA 20-281). In a T-con held in August 8,2001, FDA and sponsor reached agreement in most issues regarding ULTRAM. In T-conferences held in August 14 and 15, 2001, agreement was reached regarding the acetaminophen component, the Adverse Event table, PK and clinical studies sections.

Main issues under discussion during a T-con in August 15, 2001 were:

1. Inclusion of the description of the absorption of ULTRACET as "rapid"

   Reviewer's comment: The term "rapid" is subjective and does not add to the pharmacokinetic descriptions.

2. Inclusion of the following sentence in the clinical study section of tramadol: "The onset of pain relief after ULTRACET was consistently less than 30 minutes"

The sponsor references three pain studies in the dental pain model, in which the time to perceptible pain relief for ULTRACET was between 23 and 28 minutes (see Table 1).

Table 1. Median time (minutes) to onset of perceptible pain relief in pivotal single-dose (two tablets) dental pain studies of ULTRACET*. (source: Sponsor's table 9a of submitted 8/15/01).

Treatment	TRAMAP-ANAG 010	TRAMAP-ANAG 012	TRAMAP-ANAG 013
Tramadol/APAP	27.9	26.1	21.1
Tramadol 75 mg	30.7	52.4	74.3
APAP 650 mg	25.4	29.8	23.5
Ibuprofen 400 mg	38.6	48.7	27.1
Placebo	43.5	not estimable	not estimable

* Each tablet of ULTRACET contains tramadol 75 mg and acetaminophen 325 mg.

Reviewer's comment: Median time to perceptible pain relief (MTPPR) is one of the parameters used to determine the efficacy profile of an analgesic. Of note, the onset of pain relief for APAP alone in these studies is also less than 30 minutes. MTPPR is a very valuable parameter in the context of a particular study, relative to placebo and the active comparator. However, it is not appropriate for inclusion in labeling because:

- *TPPR does not give the complete picture of the analgesic efficacy. In this case it would suggest that all patients improved within 30 min, when some patients had no pain relief at all.*

- *It would lead to inappropriate cross-comparisons between studies of other analgesics. Other studies may have a completely different population, with different demographics or different pain intensity at baseline that could affect the outcome. Placebo or the active comparator may behave differently in different studies.*

- *Currently, the review division considers onset of analgesia within one hour to be a necessary component of an acute systemic analgesic. Therefore such a statement is appropriate for labeling. Below this threshold, descriptions of findings within specific models and studies is subject to excessive variability and is not appropriate for labeling.*

This reviewer recommends that the final label for the Clinical Study section of the label read:

Single Dose Studies for Treatment of Acute Pain

In pivotal single-dose studies in acute pain, two tablets of ULTRACET administered to patients with pain following oral surgical procedures provided greater relief than placebo or either of the individual components given at the same dose. The onset of pain relief after ULTRACET was faster than tramadol alone. Onset of analgesia occurred in less than one hour. The duration of pain relief after ULTRACET was longer than acetaminophen alone. Analgesia was generally comparable to that of the comparator, ibuprofen.

2) Recommendation for regulatory action:

NDA 21-123 should be Approved for the short term management of acute pain.

ULTRACET label is attached (Attachment 2).

Maria Lourdes Villalba, M.D., Medical Officer, HFD-550

Lawrence Goldkindl, M.D., Deputy Director, HFD-550

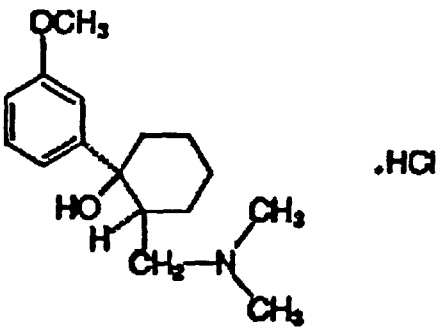
Cc: HFD-550 Division File
HDF-550/ CChen/ ROsterberg
HFD-550/ SLee/ DBashaw
HFD-550/ MWalling/BGould

ULTRACET (tramadol hydrochloride/ acetaminophen tablets)

DESCRIPTION

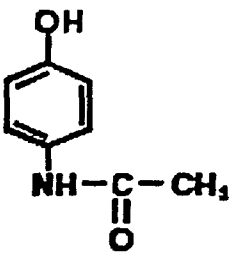
ULTRACET™ (37.5 mg tramadol hydrochloride/ 325 mg acetaminophen tablets) combines two analgesics, tramadol and acetaminophen.

The chemical name for tramadol hydrochloride is (±)cis-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride. Its structural formula is:



The molecular weight of tramadol hydrochloride is 299.84. Tramadol hydrochloride is a white, bitter, crystalline and odorless powder.

The chemical name for acetaminophen is N-acetyl-p-aminophenol. It's structural formula is:



The molecular weight of acetaminophen is 151.17. Acetaminophen is an analgesic and antipyretic agent which occurs as a white, odorless, crystalline powder, possessing a slightly bitter taste.

ULTRACET Tablets contain 37.5 mg tramadol hydrochloride and 325 mg acetaminophen and are light yellow in color. Inactive ingredients in the tablet are powdered cellulose, pregelatinized starch, sodium starch glycolate, starch, purified water, magnesium stearate, OPADRY® Light Yellow, and carnauba wax.

CLINICAL PHARMACOLOGY

The following information is based on studies of tramadol alone or acetaminophen alone, except where otherwise noted:

Pharmacodynamics

Tramadol is a centrally acting synthetic opioid analgesic. Although its mode of action is not completely understood, from animal tests, at least two complementary mechanisms appear applicable: binding of parent and M1 metabolite to μ-opioid receptors and weak inhibition of reuptake 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 opiate 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, Pharmacokinetics).

Tramadol has been shown to inhibit reuptake of norepinephrine and serotonin in vitro, as have some other opioid analgesics. These mechanisms may contribute independently to the overall analgesic profile of tramadol.

Apart from analgesia, tramadol administration may produce a constellation of symptoms (including dizziness, somnolence, nausea, constipation, sweating and pruritus) similar to that of other opioids.

Acetaminophen

Acetaminophen is a non-opiate, non-salicylate analgesic.

Pharmacokinetics

Tramadol is administered as a racemate and both the [-] and [+] forms of both tramadol and M1 are detected in the circulation. The pharmacokinetics of plasma tramadol and acetaminophen following oral administration of one ULTRACET tablet are shown in Table 1. Tramadol has a slower absorption and longer half-life when compared to acetaminophen.

Table 1: Summary of Mean (±SD) Pharmacokinetic Parameters of the (+)- and (-) Enantiomers of Tramadol and M1 and Acetaminophen Following A Single Oral Dose Of One Tramadol/Acetaminophen Combination Tablet (37.5 mg/325 mg) in Volunteers

Parameter[a]	(+)-Tramadol		(-)-Tramadol		(+)-M1		(-)-M1		acetaminophen	
C_{max} (ng/mL)	64.3	(9.3)	55.5	(8.1)	10.9	(5.7)	12.8	(4.2)	4.2	(0.8)
t_{max} (h)	1.8	(0.6)	1.8	(0.7)	2.1	(0.7)	2.2	(0.7)	0.9	(0.7)
CL/F (mL/min)	588	(226)	736	(244)	-	-	-	-	365	(84)
$t_{1/2}$ (h)	5.1	(1.4)	4.7	(1.2)	7.8	(3.0)	6.2	(1.6)	2.5	(0.6)

[a] For acetaminophen, C_{max} was measured as μg/mL.

A single dose pharmacokinetic study of ULTRACET in volunteers showed no drug interactions between tramadol and acetaminophen. Upon multiple oral dosing to steady state, however, the bioavailability of tramadol and metabolite M1 was lower for the combination tablets compared to tramadol administered alone. The decrease in AUC was 14% for (+)-tramadol, 10.4% for (-)-tramadol, 11.9% for (+)-M1 and 24.2% for (-)-M1. The cause of this reduced bioavailability is not clear. Following single or multiple dose administration of ULTRACET, no significant change in acetaminophen pharmacokinetics was observed when compared to acetaminophen given alone.

Absorption:

The absolute bioavailability of tramadol from ULTRACET tablets has not been determined. Tramadol hydrochloride has a mean absolute bioavailability of approximately 75% following administration of a single 100 mg oral dose of ULTRAM® tablets. The mean peak plasma concentration of racemic tramadol and M1 after administration of two ULTRACET tablets occurs at approximately two and three hours, respectively, post-dose.

Peak plasma concentrations of acetaminophen occur within one hour and are not affected by co-administration with tramadol. Oral absorption of acetaminophen following administration of ULTRACET occurs primarily in the small intestine.

Food Effects:

When ULTRACET was administered with food, the time to peak plasma concentration was delayed for approximately 35 minutes for tramadol and almost one hour for acetaminophen. However, peak plasma concentration or the extent of absorption of either tramadol or acetaminophen were not affected. The clinical significance of this difference is unknown.

Distribution:

The volume of distribution of tramadol was 2.6 and 2.9 L/kg in male and female subjects, respectively, following a 100 mg intravenous dose. The binding of tramadol to human plasma proteins is approximately 20% and binding also appears to be independent of concentration up to 10 µg/mL. Saturation of plasma protein binding occurs only at concentrations outside the clinically relevant range.

Acetaminophen appears to be widely distributed throughout most body tissues except fat. Its apparent volume of distribution is about 0.9 L/kg. A relative small portion (~20%) of acetaminophen is bound to plasma protein.

Metabolism:

Following oral administration, tramadol is extensively metabolized by a number of pathways, including CYP2D6 and CYP3A4, as well as by conjugation of parent and metabolites. Approximately 30% of the dose is excreted in the urine as unchanged drug, whereas 60% of the dose is excreted as metabolites. The major metabolic pathways appear to be *N*- and *O*- demethylation and glucuronidation or sulfation in the liver. Metabolite M1 (*O*-desmethyltramadol) is pharmacologically active in animal models. Formation of M1 is dependent on CYP2D6 and as such is subject to inhibition, which may affect the therapeutic response (see PRECAUTIONS – Drug Interactions).

Approximately 7% of the population has reduced activity of the CYP2D6 isoenzyme of cytochrome P450. These individuals are "poor metabolizers" of debrisoquine, dextromethorphan, tricyclic antidepressants, among other drugs. Based on a population PK analysis of Phase 1 studies in healthy subjects, concentrations of tramadol were approximately 20% higher in "poor metabolizers" versus "extensive metabolizers", while M1 concentrations were 40% lower. In vitro drug interaction studies in human liver microsomes indicates that inhibitors of CYP2D6 such as fluoxetine and its metabolite norfluoxetine, amitriptyline and quinidine inhibit the metabolism of tramadol to various degrees. The full pharmacological impact of these alterations in terms of either efficacy or safety is unknown. Concomitant use of SEROTONIN re-uptake INHIBITORS and MAO INHIBITORS may enhance the risk of adverse events, including seizure (see WARNINGS) and serotonin syndrome.

Acetaminophen is primarily metabolized in the liver by first-order kinetics and involves three principal separate pathways:

a) conjugation with glucuronide;

b) conjugation with sulfate; and

c) oxidation via the cytochrome, P450-dependent, mixed-function oxidase enzyme pathway to form a reactive intermediate metabolite, which conjugates with glutathione and is then further metabolized to form cysteine and mercapturic acid conjugates. The principal cytochrome P450 isoenzyme involved appears to be CYP2E1, with CYP1A2 and CYP3A4 as additional pathways.

In adults, the majority of acetaminophen is conjugated with glucuronic acid and, to a lesser extent, with sulfate. These glucuronide-, sulfate-, and glutathione-derived metabolites lack biologic activity. In premature infants, newborns, and young infants, the sulfate conjugate predominates.

Elimination

Tramadol is eliminated primarily through metabolism by the liver and the metabolites are eliminated primarily by the kidneys. The plasma elimination half-lives of racemic tramadol and M1 are approximately 5-6 and 7 hours, respectively, after administration of ULTRACET. The apparent plasma elimination half-life of racemic tramadol increased to 7-9 hours upon multiple dosing of ULTRACET.

The half-life of acetaminophen is about 2 to 3 hours in adults. It is somewhat shorter in children and somewhat longer in neonates and in cirrhotic patients. Acetaminophen is eliminated from the body primarily by formation of glucuronide and sulfate conjugates in a dose-dependent manner. Less than 9% of acetaminophen is excreted unchanged in the urine.

Special Populations

Renal:

The pharmacokinetics of ULTRACET in patients with renal impairment have not been studied. Based on studies using tramadol alone, excretion of tramadol and metabolite M1 is reduced in patients with creatinine clearance of less than 30 mL/min, adjustment of dosing regimen in this patient population is recommended. (See DOSAGE AND ADMINISTRATION). The total amount of tramadol and M1 removed during a 4-hour dialysis period is less than 7% of the administered dose based on studies using tramadol alone.

Hepatic:

The pharmacokinetics and tolerability of ULTRACET in patients with impaired hepatic function has not been studied. Since tramadol and acetaminophen are both extensively metabolized by the liver, the use of ULTRACET in patients with hepatic impairment is not recommended (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Geriatric:

A population pharmacokinetic analysis of data obtained from a clinical trial in patients with chronic pain treated with ULTRACET which included 55 patients between 65 and 75 years of age and 19 patients over 75 years of age, showed no significant changes in pharmacokinetics of tramadol and acetaminophen in elderly patients with normal renal and hepatic function (See PRECAUTIONS: Geriatric Use).

Gender:

Tramadol clearance was 20% higher in female subjects compared to males on four phase I studies of ULTRACET in 50 male and 34 female healthy subjects. The clinical significance of this difference is unknown.

Pediatric:

Pharmacokinetics of ULTRACET Tablets have not been studied in pediatric patients below 16 years of age.

Clinical Studies

Single Dose Studies for Treatment of Acute Pain

In pivotal single-dose studies in acute pain, two tablets of ULTRACET administered to patients with pain following oral surgical procedures provided greater relief than placebo or either of the individual components given at the same dose. The onset of pain relief after ULTRACET was faster than tramadol alone. Onset of analgesia occurred in less than one hour. The duration of pain relief after ULTRACET was longer than acetaminophen alone. Analgesia was generally comparable to that of the comparator, ibuprofen.

INDICATIONS AND USAGE

ULTRACET is indicated for the short-term (five days or less) management of acute pain.

CONTRAINDICATIONS

ULTRACET should not be administered to patients who have previously demonstrated hypersensitivity to tramadol, acetaminophen, any other component of this product or opioids. ULTRACET is contraindicated in any situation where opioids are contraindicated, including acute intoxication with any of the following: alcohol, hypnotics, narcotics, centrally acting analgesics, opioids or psychotropic drugs. ULTRACET may worsen central nervous system and respiratory depression in these patients.

WARNINGS

Seizure Risk

Seizures have been reported in patients receiving tramadol within the recommended dosage range. Spontaneous post-marketing reports indicate that seizure risk is increased with doses of tramadol above the recommended range. Concomitant use of tramadol increases the seizure risk in patients taking:

- **Selective serotonin reuptake inhibitors (SSRI antidepressants or anorectics),**
- **Tricyclic antidepressants (TCAs), and other tricyclic compounds (e.g., cyclobenzaprine, promethazine, etc.), or**

- **Other opioids.**

Administration of tramadol may enhance the seizure risk in patients taking:

- **MAO inhibitors (see also WARNINGS – Use with MAO Inhibitors),**
- **Neuroleptics, or**
- **Other drugs that reduce the seizure threshold.**

Risk of convulsions may also increase in patients with epilepsy, those with a history of seizures, or in patients with a recognized risk for seizure (such as head trauma, metabolic disorders, alcohol and drug withdrawal, CNS infections). In tramadol overdose, naloxone administration may increase the risk of seizure.

Anaphylactoid Reactions

Serious and rarely fatal anaphylactoid reactions have been reported in patients receiving therapy with tramadol. When these events do occur it is often following the first dose. Other reported allergic reactions include pruritus, hives, bronchospasm, angioedema, toxic epidermal necrolysis and Stevens-Johnson syndrome. Patients with a history of anaphylactoid reactions to codeine and other opioids may be at increased risk and therefore should not receive ULTRACET (see CONTRAINDICATIONS).

Respiratory Depression

Administer ULTRACET cautiously in patients at risk for respiratory depression. In these patients, alternative non-opioid analgesics should be considered. When large doses of tramadol are administered with anesthetic medications or alcohol, respiratory depression may result. Respiratory depression should be treated as an overdose. If naloxone is to be administered, use cautiously because it may precipitate seizures (see WARNINGS, Seizure Risk and OVERDOSAGE).

Interaction with Central Nervous System (CNS) Depressants

ULTRACET should be used with caution and in reduced dosages when administered to patients receiving CNS depressants such as alcohol, opioids, anesthetic agents, narcotics, phenothiazines, tranquilizers or sedative hypnotics. Tramadol increases the risk of CNS and respiratory depression in these patients.

Increased Intracranial Pressure or Head Trauma

ULTRACET should be used with caution in patients with increased intracranial pressure or head injury. The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure and may be markedly exaggerated in these patients. Additionally, pupillary changes (miosis) from tramadol may obscure the existence, extent, or course of intracranial pathology. Clinicians should

also maintain a high index of suspicion for adverse drug reaction when evaluating altered mental status in these patients if they are receiving ULTRACET (see Respiratory Depression).

Use in Ambulatory Patients

Tramadol may impair the mental and or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using this drug should be cautioned accordingly.

Use with MAO Inhibitors and Serotonin re-uptake inhibitors

Use ULTRACET with great caution in patients taking monoamine oxidase inhibitors. Animal studies have shown increased deaths with combined administration of MAO inhibitors and tramadol. Concomitant use of tramadol with MAO inhibitors or SSRI's increases the risk of adverse events, including seizure and serotonin syndrome.

Use with Alcohol

ULTRACET should not be used concomitantly with alcohol consumption. The use of ULTRACET in patients with liver disease is not recommended.

Use with Other Acetaminophen-containing Products

Due to the potential for acetaminophen hepatotoxicity at doses higher than the recommended dose, ULTRACET should not be used concomitantly with other acetaminophen-containing products.

Withdrawal

Withdrawal symptoms may occur if ULTRACET is discontinued abruptly. (See DRUG ABUSE AND DEPENDENCE) These symptoms may include: anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhea, upper respiratory symptoms, piloerection, and rarely hallucinations. Clinical experience suggests that withdrawal symptoms may be relieved by tapering the medication.

Physical Dependence and Abuse

Tramadol may induce psychic and physical dependence of the morphine-type (μ-opioid). (See DRUG ABUSE AND DEPENDENCE). Tramadol should not be used in opioid-dependent patients. Tramadol has been shown to reinitiate physical dependence in some patients that have been previously dependent on other opioids. Dependence and abuse, including drug-seeking behavior and taking illicit actions to obtain the drug are not limited to those patients with prior history of opioid dependence.

Risk of Overdosage

Serious potential consequences of overdosage with tramadol are central nervous system depression, respiratory depression and death. In treating an overdose, primary attention

should be given to maintaining adequate ventilation along with general supportive treatment. (See OVERDOSAGE).

- Serious potential consequences of overdosage with acetaminophen are hepatic (centrilobular) necrosis, leading to hepatic failure and death. Emergency help should be sought immediately and treatment initiated immediately if overdose is suspected, even if symptoms are not apparent.

PRECAUTIONS

General

The recommended dose of ULTRACET should not be exceeded.

Do not co-administer ULTRACET with other tramadol or acetaminophen-containing products. (See WARNINGS, Use with other Acetaminophen-containing Products and Risk of Overdosage).

Pediatric Use

The safety and effectiveness of ULTRACET has not been studied in the pediatric population.

Geriatric Use

In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function; of concomitant disease and multiple drug therapy.

Acute Abdominal Conditions

The administration of ULTRACET may complicate the clinical assessment of patients with acute abdominal conditions.

Use in Renal Disease

ULTRACET has not been studied in patients with impaired renal function. Experience with tramadol suggest that impaired renal function results in a decreased rate and extent of excretion of tramadol and its active metabolite, M1. In patients with creatinine clearances of less than 30 mL/min, it is recommended that the dosing interval of ULTRACET be increased not to exceed 2 tablets every 12 hours.

Use in Hepatic Disease

ULTRACET has not been studied in patients with impaired hepatic function. The use of ULTRACET in patients with hepatic impairment is not recommended (See WARNINGS, Use with alcohol).

Information for Patients

- ULTRACET may impair mental or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.
- ULTRACET should not be taken with alcohol containing beverages.
- The patient should be instructed not to take ULTRACET in combination with other tramadol or acetaminophen-containing products, including over-the-counter preparations.
- ULTRACET should be used with caution when taking medications such as tranquilizers, hypnotics or other opiate containing analgesics.
- The patient should be instructed to inform the physician if they are pregnant, think they might become pregnant, or are trying to become pregnant (see PRECAUTIONS: Labor and Delivery).
- The patient should understand the single-dose and 24-hour dose limit and the time interval between doses, since exceeding these recommendations can result in respiratory depression, **seizures, hepatic toxicity and death.**

Drug Interactions

In vitro studies indicate that tramadol is unlikely to inhibit the CYP3A4-mediated metabolism of other drugs when tramadol is administered concomitantly at therapeutic doses. Tramadol does not appear to induce its own metabolism in humans, since observed maximal plasma concentrations after multiple oral doses are higher than expected based on single-dose data. Tramadol is a mild inducer of selected drug metabolism pathways measured in animals.

Use with Carbamazepine

Patients taking carbamazepine may have a significantly reduced analgesic effect of tramadol. Because carbamazepine increases tramadol metabolism and because of the seizure risk associated with tramadol concomitant administration of ULTRACET and carbamazepine is not recommended.

Use with Quinidine

Tramadol is metabolized to M1 by CYP2D6. Quinidine is a selective inhibitor of that isoenzyme; so that concomitant administration of quinidine and tramadol results in increased concentrations of tramadol and reduced concentrations of M1. The clinical

consequences of these findings are unknown. In vitro drug interaction studies in human liver microsomes indicate that tramadol has no effect on quinidine metabolism.

Use with Inhibitors of CYP2D6

In vitro drug interaction studies in human liver microsomes indicate that concomitant administration with inhibitors of CYP2D6 such as fluoxetine, paroxetine, and amitriptyline could result in some inhibition of the metabolism of tramadol.

Use with Cimetidine

Concomitant administration of ULTRACET and cimetidine has not been studied. Concomitant administration of tramadol and cimetidine does not result in clinically significant changes in tramadol pharmacokinetics. Therefore, no alteration of the ULTRACET dosage regimen is recommended.

Use with MAO Inhibitors

Interactions with MAO Inhibitors, due to interference with detoxification mechanisms, have been reported for some centrally acting drugs (see WARNINGS, Use with MAO Inhibitors).

Use with Digoxin

Post-marketing surveillance of tramadol has revealed rare reports of digoxin toxicity.

Use with Warfarin Like Compounds

Post-marketing surveillance of both tramadol and acetaminophen individual products have revealed rare alterations of warfarin effect, including elevation of prothrombin times.

While such changes have been generally of limited clinical significance for the individual products, periodic evaluation of prothrombin time should be performed when ULTRACET and warfarin-like compounds are administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility

There are no animal or laboratory studies on the combination product (tramadol and acetaminophen) to evaluate carcinogenesis, mutagenesis, or impairment of fertility.

A slight but statistically significant increase in two common murine tumors, pulmonary and hepatic, was observed in a mouse carcinogenicity study, particularly in aged mice. Mice were dosed orally up to 30 mg/kg (90 mg/m^2 or 0.5 times the maximum daily human tramadol dosage of 185 mg/m^2) 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 such finding occurred in rat carcinogenicity study (dosing orally up to 30 mg/kg, 180 mg/m^2, or 1 time the maximum daily human tramadol dosage).

Tramadol was not mutagenic in the following assays: Ames Salmonella microsomal activation test, CHO/HPRT mammalian cell assay, mouse lymphoma assay (in the absence of metabolic activation), dominant lethal mutation tests in mice, chromosome aberration test in Chinese hamsters, and bone marrow micronucleus tests in mice and Chinese hamsters. Weakly mutagenic results occurred in the presence of metabolic activation in the mouse lymphoma assay and micronucleus test in rats. Overall, the weight of evidence from these tests indicates that tramadol does not pose a genotoxic risk to humans.

No effects on fertility were observed for tramadol at oral dose levels up to 50 mg/kg (350 mg/m^2) in male rats and 75 mg/kg (450 mg/m^2) in female rats. These dosages are 1.6 and 2.4 times the maximum daily human tramadol dosage of 185 mg/m^2.

Pregnancy

Teratogenic Effects: *Pregnancy Category C*

No drug-related teratogenic effects were observed in the progeny of rats treated orally with tramadol and acetaminophen. The tramadol/ acetaminophen combination product was shown to be embryotoxic and fetotoxic in rats at a maternally toxic dose, 50/434 mg/kg tramadol/acetaminophen (300/2604 mg/m^2 or 1.6 times the maximum daily human tramadol/acetaminophen dosage of 185/1591 mg/m^2), but was not teratogenic at this dose level. Embryo and fetal toxicity consisted of decreased fetal weights and increased supernumerary ribs.

Non-teratogenic effects:

Tramadol alone was evaluated in peri- and post-natal studies in rats. Progeny of dams receiving oral (gavage) dose levels of 50 mg/kg (300 mg/m^2 or 1.6 times the maximum daily human tramadol dosage) or greater had decreased weights, and pup survival was decreased early in lactation at 80 mg/kg (480 mg/m^2 or 2.6 times the maximum daily human tramadol dosage).

There are no adequate and well-controlled studies in pregnant women. ULTRACET should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Neonatal seizures, neonatal withdrawal syndrome, fetal death and still birth have been reported with tramadol hydrochloride during post-marketing.

Labor and Delivery

ULTRACET should not be used in pregnant women prior to or during labor unless the potential benefits outweigh the risks. Safe use in pregnancy has not been established. Chronic use during pregnancy may lead to physical dependence and post-partum withdrawal symptoms in the newborn. (See DRUG ABUSE AND DEPENDENCE) Tramadol has been shown to cross the placenta. The mean ratio of serum tramadol in the umbilical veins compared to maternal veins was 0.83 for 40 women given tramadol during labor.

The effect of ULTRACET, if any, on the later growth, development, and functional maturation of the child is unknown.

Nursing Mothers

ULTRACET is not recommended for obstetrical preoperative medication or for post-delivery analgesia in nursing mothers because its safety in infants and newborns has not been studied.

Following a single IV 100 mg dose of tramadol, the cumulative excretion in breast milk within 16 hours post-dose was 100 μg of tramadol (0.1% of the maternal dose) and 27 μg of M1.

ADVERSE REACTIONS

Table 2 reports the incidence rate of treatment-emergent adverse events over five days of ULTRACET use in clinical trials (subjects took an average of at least 6 tablets per day).

Table 2: Incidence of Treatment-Emergent Adverse Events (≥2.0%)

Body System Preferred Term	ULTRACET (N=142) (%)
Gastrointestinal System Disorders	
Constipation	6
Nausea	3
Diarrhea	3
Dry Mouth	2
Psycchiatric Disorders	
Somnolence	6
Anorexia	3
Insomnia	2
Central & Peripheral Nervous System	
Dizziness	3
Skin and Appendages	
Sweating Increased	4
Pruritus	2
Reproductive Disorders, Male *	
Prostatic Disorder	2

* Number of males = 62

Incidence at least 1%, causal relationship at least possible or greater: the following lists adverse reactions that occurred with an incidence of at least 1% in single-dose or repeated-dose clinical trials of ULTRACET.

Body as a Whole – Asthenia, fatigue, hot flushes

Central and Peripheral Nervous System – Dizziness, headache, tremor

Gastrointestinal System – Abdominal pain, constipation, diarrhea, dyspepsia, flatulence, dry mouth, nausea, vomiting

Psychiatric Disorders – Anorexia, anxiety, confusion, euphoria, insomnia, nervousness, somnolence

Skin and Appendages – Pruritus, rash, increased sweating.

Selected Adverse events occurring at less than 1%: the following lists clinically relevant adverse reactions that occurred with an incidence of less than 1% in ULTRACET clinical trials .

Body as a Whole – Chest pain, rigors, syncope, withdrawal syndrome

Cardiovascular Disorders – Hypertension, aggravated hypertension, hypotension

Central and Peripheral Nervous System – Ataxia, convulsions, hypertonia, migraine, aggravated migraine, involuntary muscle contractions, paraesthesia, stupor, vertigo

Gastrointestinal System – Dysphagia, melena, tongue edema

Hearing and Vestibular Disorders – Tinnitus

Heart Rate and Rhythm Disorders – Arrhythmia, palpitation, tachycardia

Liver and Biliary System – Hepatic function abnormal

Metabolic and Nutritional Disorders – Weight decrease

Psychiatric Disorders – Amnesia, depersonalization, depression, drug abuse, emotional lability, hallucination, impotence, paroniria, abnormal thinking

Red Blood Cell Disorders – Anemia

Respiratory System – Dyspnea

Urinary System – Albuminuria, micturition disorder, oliguria, urinary retention

Vision Disorders – Abnormal vision

Other clinically significant adverse experiences previously reported with tramadol hydrochloride.

Other events which have been reported with the use of tramadol products and for which a causal association has not been determined include: vasodilation, orthostatic hypotension, myocardial ischemia, pulmonary edema, allergic reactions (including anaphylaxis and urticaria, Stevens Johnson Syndrome/TENS), cognitive dysfunction, difficulty concentrating, depression, suicidal tendency, hepatitis liver failure and gastrointestinal bleeding. Reported laboratory abnormalities included elevated creatinine and liver function tests. Serotonin syndrome (whose symptoms may include mental status change, hyperreflexia, fever, shivering tremor, agitation, diaphoresis, seizures and coma) has been reported with tramadol when used concomitantly with other serotonergic agents such as SSRIs and MAOIs.

Other clinically significant adverse experiences previously reported with acetaminophen.

Allergic reactions (primarily skin rash) or reports of hypersensitivity secondary to acetaminophen are rare and generally controlled by discontinuation of the drug and, when necessary, symptomatic treatment.

DRUG ABUSE AND DEPENDENCE

Tramadol may induce psychic and physical dependence of the morphine-type (μ-opioid) (See WARNING). Dependence and abuse, including drug-seeking behavior and taking illicit actions to obtain the drug are not limited to those patients with a prior history of opioid dependence. The risk in patients with substance abuse has been observed to be higher. Tramadol is associated with craving and tolerance development. Withdrawal symptoms may occur if tramadol is discontinued abruptly. These symptoms may include: anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhea, upper respiratory symptoms, piloerection, and rarely hallucinations. Clinical experience suggests that withdrawal symptoms may be relieved by reinstitution of opioid therapy followed by a gradual, tapered dose reduction of the medication combined with symptomatic support.

OVERDOSAGE

ULTRACET is a combination product. The clinical presentation of overdose may include the signs and symptoms of tramadol toxicity, acetaminophen toxicity or both. The initial symptoms of tramadol overdosage may include respiratory depression and or seizures. The initial symptoms seen within the first 24 hours following an acetaminophen overdose are: anorexia, nausea, vomiting, malaise, pallor and diaphoresis.

Tramadol

Serious potential consequences of overdosage are respiratory depression, lethargy, coma seizure, cardiac arrest and death. (See WARNING). Fatalities have been reported in post marketing in association with both intentional and unintentional overdose with tramadol.

Acetaminophen

Serious potential consequences of overdosage with acetaminophen are hepatic centrilobular necrosis, leading to hepatic failure and death. Renal tubular necrosis, hypoglycemia and coagulation defects also may occur. Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post ingestion.

Treatment of Overdose

A single or multiple overdose with ULTRACET may be a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended.

In treating an overdose of ULTRACET, primary attention should be given to maintaining adequate ventilation along with general supportive treatment. While naloxone will reverse some, but not all, symptoms caused by overdosage with tramadol, the risk of seizures is also increased with naloxone administration. In animals, convulsions

following the administration of toxic doses of tramadol could be suppressed with barbiturates or benzodiazepines but were increased with naloxone. Naloxone administration did not change the lethality of an overdose in mice. Based on experience with tramadol, hemodialysis is not expected to be helpful in an overdose because it removes less than 7% of the administered dose in a 4-hour dialysis period.

Standard recommendations should be followed for the treatment of acetaminophen overdose.

DOSAGE AND ADMINISTRATION

For the short-term (five days or less) management of acute pain, the recommended dose of ULTRACET is 2 tablets every 4 to 6 hours as needed for pain relief up to a maximum of 8 tablets per day.

Individualization of Dose

In patients with creatinine clearances of less than 30 mL/min, it is recommended that the dosing interval of ULTRACET be increased not to exceed 2 tablets every 12 hours. Dose selection for an elderly patient should be cautious, in view of the potential for greater sensitivity to adverse events.

HOW SUPPLIED

ULTRACET (37.5 mg tramadol hydrochloride/ 325 mg acetaminophen) Tablets (light yellow, film-coated capsule-shaped tablet) debossed "O-M" on one side and "650" on the other are available as follows:

20's: NDC 0045 0650 50 (Bottles of 20 tablets)

100's: NDC 0045 0650 60 (Bottles of 100 tablets).

500's: NDC 0045 0650 70 (Bottles of 500 tablets).

HUD 100's: NDC 0045 0650 10 (Packages of 100 unit doses in blister packs, 10 cards of 10 tablets each).

Dispense in a tight container. Store at 25°C (77°F); excursions permitted to 15 – 30°C (59 - 86°F).

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