



APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS, ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

3004 '01 OCT 25 P2:14

October 24, 2001

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1-23
12420 Parklawn Drive
Rockville, MD 20857

CITIZEN'S PETITION

This citizen's petition is submitted by Apotex Corp pursuant to section 505 (j) of the Federal Food, Drug and Cosmetic Act and 21 CFR 10.25 (a), 10.30, 314.122 and 314.161.¹ This petition requests that the Food and Drug Administration (FDA) determine that the 50 mg to 100 mg dosing to be administered as needed for relief every four to six hours, not to exceed 400 mg per day regimen for the listed drug Ultram® tablets was not withdrawn from the labeling for reasons of safety or effectiveness, and that the inclusion of that dosing regimen in a generic drug product does not render it less safe or effective than Ultram tablets. Therefore, TorPharm's abbreviated new drug application (ANDA) 75-981 may reference the discontinued dosage schedule for labeling purposes.

A. Action Requested

Apotex Corp requests FDA make a determination that Ultram's sponsor did not discontinue the 50 mg to 100 mg every four to six hours not to exceed 400 mg per day dosing schedule from the drug product's labeling due to safety or effectiveness reasons. Apotex Corp. requests FDA make a determination that omission of the titrated dosage regimen and usage of the 50 mg to 100 mg dosing schedule would not render the proposed generic drug product less safe or effective than the currently marketed innovator product. Apotex Corp. further requests FDA then make a determination that TorPharm's ANDA based on Ultram tablets may include the discontinued labeling that was previously FDA-approved.

¹ On October 26, 2000, FDA published a "Draft Guidance for industry on Referencing Discontinued Labeling for Listed Drugs in Abbreviated New Drug Applications." 65 Fed. Reg. 64225. Although the draft guidance is consistent with the relief sought, this citizen petition is submitted pursuant to the above-listed statute and regulations, not pursuant to the draft guidance.

010.0495

081

B. Statement of Grounds

Apotex Corp is the US agent for its corporate affiliate TorPharm. TorPharm is the sponsor of pending ANDA 75-981 which references the listed drug Ultram tablets. The generic form of Ultram tablets is known as tramadol. TorPharm submitted its ANDA in order to manufacture tablets containing 50 mg of tramadol. Tramadol is indicated for the management of moderate to moderately severe pain in adults.

The NDA for Ultram tablets is held by RW Johnson. The product received final approval March 3, 1995. On August 21, 1998, RW Johnson received approval for a titrated dosage schedule change denominated in the "Orange Book" as D-44; "in a clinical trial, fewer discontinuations due to adverse events, especially dizziness and vertigo, were observed when titrating the dose in increments of 50 mg/day every three days until an effective dose (not exceeding 400 mg/day) was reached." The FDA medical review report for this titrated dosage schedule does not indicate that the change was made in response to any concerns regarding the safety or efficacy of the original 50 mg or 100 mg dosing regimen (copy attached). This titrated dosing schedule was granted 3-year market exclusivity (expired August 21, 2001) but then later had a pediatric exclusivity extension attached to it to expire February 21, 2002.

TorPharm submitted its ANDA on August 29, 2000 with a statement that their proposed labeling does not include the titrated dosing schedule covered by the exclusivity code D-44.

On December 23, 1999, RW Johnson received approval for another titrated dosing regimen represented by exclusivity D-63; "to allow a titration dosing regimen using a 25 mg dose." This dosing schedule too was granted 3-year market exclusivity to expire December 23, 2002 and an additional pediatric exclusivity to expire June 23, 2002. The FDA medical review report for this titrated dosage schedule does not indicate that the change was made in response to any concerns regarding the safety or efficacy of the titration regimen (copy attached).

On March 8, 2001, FDA requested TorPharm to update their exclusivity statement to address the D-63. On May 10, 2001, TorPharm did so by submitting a certification stating that their labeling did not include the dosing schedule covered by the D-63 exclusivity code.

On September 4, 2001 FDA notified TorPharm that they acknowledged that TorPharm did not seek approval of labeling that includes the new dosing schedule protected by the D-44 and D-63 exclusivities. However, pending resolution of issues regarding the differences between TorPharm's proposed dosing information for its drug product and that information in the last approved for the reference listed drug, Ultram, FDA deferred comment at this time.

Referencing Discontinued Labeling

The Drug Price Competition and Patent Term Restoration Act of 1984 (known as the Hatch-Waxman Amendments) created a framework for patent term extensions and non-patent exclusivity periods for brand name drug products and a system for speeding FDA's approval of generic drug products. One provision of the Hatch-Waxman Amendments requires that an ANDA must provide information to show that the labeling proposed for the generic drug product is the "same as the labeling approved for the listed drug," with minor exceptions not relevant to this petition. 21 U.S.C. section 355(j)(2)(A)(v). While there is no final agency guidance regarding the exact situation presented here, other areas of the statute and regulations demonstrate how FDA deals with similar situations.²

When an ANDA references a drug that has been withdrawn from the marketplace, FDA may still approve the ANDA upon a determination that the withdrawal was not for safety or effectiveness reasons. 21 U.S.C. section 355 (j)(6); 21 CFR 314.122 and 314.161. Similarly, FDA is also authorized to approve an ANDA that omits in its labeling an indication or other aspect of labeling for the listed drug that is protected by patent or exclusivity (21 CFR 314.94(a)(8)(iv)). In this circumstance, omission from the NDA's labeling of protected aspects is allowed if the omission does not render the generic drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use. 21 CFR 314.127(a)(7).

In conformance with the above referenced provisions, FDA should make a determination that the Ultram tablets labeling that references 50 mg to 100 mg every 4-6 hours dosing was not withdrawn for safety or effectiveness reasons. FDA should also determine that omission of the currently protected information in the labeling will not render TorPharm's generic drug product less safe or effective than the currently marketed Ultram tablets product. Upon such determinations, FDA should allow TorPharm's ANDA to reference the discontinued labeling and allow final approval.

Safety and Effectiveness of the Original Dosing Schedule

(50 mg to 100 mg administered for relief every four to six hours not to exceed 400 mg per day).

There is no documentation that the old dosing regime was discontinued for safety or efficacy reasons. In fact, if immediate pain relief is needed, the medical examiner suggested that the old regime would be more appropriate than the new titration regime.

² The issue addressed by this petition is not one for which a suitability petition may be filed. 21 CFR 314.93.

The stated intent of the manufacturer in changing the dosing schedule was to reduce the incidence of discontinued drug usage, not concerns for safety or effectiveness of the dosing schedule. However, it is widely acknowledged that brand name drug companies make labeling changes in an attempt to secure exclusivity and delay competition-an "intent" that has little to do with the safety and efficacy of the old labeling. FDA has agreed that a "patent may be a valid reason for labeling differences between the reference listed drug and the ANDA drug product and that such differences should not be a basis for refusing to approve an ANDA." 57 Fed. Reg. 17950, 17968 (April 28, 1992) (preamble finalizing 21 CFR 314.127(a)(7)) (copy enclosed).

Conclusion

This citizen petition asks that FDA make a determination that the original dosing regimen was not withdrawn for safety or effectiveness concerns and, therefore, TorPharm's ANDA can properly reference that dosing schedule for use on a generic drug product's labeling.

C. Environmental Impact

This petition is entitled to a categorical exclusion under 21 CFR 25.30 and 25.31.

D. Economic Report

Apotex Corp. will submit an economic analysis upon request.

E. Certification

The undersigned certifies that, 'to the best knowledge and belief of the undersigned, this petition includes all information and views upon which the petitioner relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

Respectfully submitted,



Marcy Macdonald
Associate Director, Regulatory Affairs
Apotex Corp.

Attachments

**Approved Package for
Dosing Schedule**

Approved August 21, 1998



DEPARTMENT OF HEALTH & HUMAN SERVICES

DF

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-281/S-014/S-015

AUG 21 1998

The R. W. Johnson Pharmaceutical Research Institute
Attention: Natasha Rogozenski
Manager, Regulatory Affairs
920 Route 202 SOUL! P.O. Box 300
Raritan, New Jersey 08869

Dear Ms. Rogozenski:

Please refer to your supplemental new drug applications dated August 11, 1997, received August 22, 1997, and dated April 9, 1998, received April 10, 1993, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ultram (tramadol hydrochloride tablets).

These supplemental new drug applications (S-014) provide for the addition of the following text in the DOSAGE AND ADMINISTRATION section of the labeling:

These supplemental new drug applications (S-015) also provide for minor administrative changes and the following change in the ADVERSE EVENTS section of the labeling:

We have completed the review of these supplemental applications and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the proposed labeling dated April 9, 1998, with the following addition to the DOSAGE AND ADMINISTRATION section:

Accordingly, these supplemental applications are approved effective on the date of this letter.

NDA 20-281/S-014/S-015
Page 2

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-281/S-014/S-015." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug ~~and~~ for patient care, we (i.e. Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact D'Annie Gunter, Project Manager, at (301) 827-2090.

Sincerely,

/s/ 8-21-98

John E. Hyde, Ph.D, M.D.
Acting Deputy Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

ND.4 20-281/S-014/S-015
Page 3

CO:

Archival NDA 20-281

HFD-550/Div. Files

HFD-550/D. Gunter

HFD-550/J. Hyde

HF-2/Med Watch (with labeling)

HFD-002/ORM (with labeling)

HFD-105/ADRA (with labeling)

HFD-40 DDMAC (with labeling)

HFD-613/OGD (with labeling)

HFD-21 ACS (with labeling) - for drug discussed at advisory committee meeting.

HFD-95 DDMS (with labeling)

HFD-830 DNDC Division Director

DISTRICT OFFICE

Drafted by: cck/August 19, 1998

Initialed by:

final:

filename: S14AP8.820

APPROVAL (AP)

DIV

MEDICAL TEAM LEADER REVIEW

AUG 21 1998

ANTI-INFLAMMATORY, ANALGESIC AND OPHTHALMIC DRUG
PRODUCTS DIVISION - HFD-550

NDA #: 20-281, SLR-014
 SUBMISSION DATE: August 21, 1997.
 TYPE: Labeling Supplement
 REVIEW DATE: August 21, 1998.
 REVIEWER: John Hyde, Ph.D., M.D.

NAME: Ultram (tramadol hydrochloride)
 APPLICANT: R.W. Johnson
 920 Route 202 South
 P.O. Box 300
 Raritan, NJ 08869

PHARMACOLOGIC CATEGORY: Analgesic
 PROPOSED INDICATIONS: Management of pain.
 DOSAGE FORM & ROUTE: Tablet 50 mg, oral.
 csu: D. Gunter

MATERIALS REVIEWED: Study report, 3 vol., submitted in
 amendment dated 8-27-97.

RESUME:

Tramadol is a synthetic compound with opioid activity. It is indicated for the management of pain. Like opioids, the more common non-serious adverse events are seen in the CNS and GI system. The two most common adverse events in the labeling are dizziness/vertigo and nausea. With opioids these symptoms generally resolve on continued therapy (but constipation usually remains a persistent problem). Therefore it is reasonable to try to investigate strategies to ameliorate these events at onset of therapy in hopes of increasing the fraction of patients that can achieve a tolerable stable regimen.

The applicant undertook a short trial comparing three rates of titration up to a stable dose of 200 mg/day. As a result, the applicant proposes amending the DOSAGE AND ADMINISTRATION section by adding the following sentence at the end:

In a letter dated 1/30/98, the division requested a labeling change to add a Boxed Warning for the seizure risk. The applicant has appealed that request, and as of the date of this review the appeal is still under consideration.

Clinical Study

Study Design

General Design

The study is a multicenter, randomized, double-blind, placebo-controlled parallel study of three different titration rates for initiating tramadol therapy on top of stable NSAID therapy in patients with osteoarthritis. Double-blind treatment lasted 14 days. A two-month open label extension was offered to completers.

Eligibility

Males or females 45 years or older with symptomatic, X-ray confirmed osteoarthritis for at least one year, who have been on a stable NSAID dose for at least 30 days and who require additional pain relief. All subjects were to be in "generally good health," and females were required to be incapable of pregnancy or to practice one of the methods of birth control specified by the study protocol.

Exclusions

- Rheumatoid arthritis; ankylosing spondylitis; active gout; trauma, infection, or avascular necrosis of the sentinel joint.
- Contraindication to tramadol or NSAID's.
- Using coumadin-type anticoagulants, lithium, methotrexate, oral hypoglycemics, phenothiazines, sedative hypnotics.
- Investigational drug use in past 30 days.
- Intraarticular steroids in past 3 months.
- Narcotic or alcohol abuse in past 12 months.
- Serum creatinine > 1.5 mg/dL.
- Pregnant or lactating females.
- Significant medical disease.

Treatment Plan

Patients were randomized to one of four treatment groups: 1-Day Titration, 4-Day Titration, 10-Day Titration or Placebo. Probability of assignment was in a ratio of 1-Day:4-Day:10-Day:Placebo = 2:2:2:1. The assigned total daily dose of tramadol for each group is given in the table below:

Total Daily Tramadol Dose by Day

Day	1-Day Titration	Titration	10-Day Titration	Placebo
1	200	50	50	0
2	200	100	50	0
3	200	150	50	0
4-6	200	200	100	0
7-9	200	200	150	0
10-14	200	200	200	0

Blinding of the different doses was achieved using a combination of 50 mg tramadol capsules and matching placebo capsules, given as capsules q.i.d. For the 50 mg dose, only the last capsule each day contained tramadol. For the 100 mg dose, the second and fourth capsules contained tramadol. For the 150 mg, all but the third capsule contained tramadol. For the 200 mg dose, all capsules contained tramadol. Medication was packaged in blister cards. The study used tramadol batch #R6023 and placebo batch #R6024.

Concomitant medication: Patients were to continue their stable dose of NSAID, but no other pain medications were permitted. If they experienced a flare for more than 24 hours, patients were permitted to use acetaminophen for 5 days or as directed by the investigator. Acetaminophen was to be discontinued at least 3 days before the final efficacy evaluation. Treatment for intercurrent conditions was permitted, but medication use had to be recorded.

An open label extension was offered to patients completing the double-blind portion. Treatment could last up to two months.

Assessment

Discontinuations: Patient could be discontinued for patient choice, protocol violation, serious adverse event, significant intercurrent illness. Reason for discontinuation was to be recorded, but there were no specific instructions in the protocol for how to assign attribution of reason for discontinuation.

Efficacy: At 14 days or the termination of the double-blind phase, patients assessed pain of the sentinel joint over the last 48 hours on a visual analogue scale. Also, both patient and investigator provided global ratings on a 5-point scale from Very Poor to Very Good.

Statistical Analysis: The primary analysis per protocol was an intent-to-treat test of the linear trend in the proportions of subjects discontinuing for nausea or vomiting, to be done using the Cochran-Armitage trend test at the 2-sided 5% significance level. No explicit secondary analyses were stated. The analysis plan also mentioned comparison of adverse event rates and summaries of laboratory tests and vital signs.

Study Results

A total of 465 patients were randomized using 28 centers. The numbers randomized to each group and the disposition of patients is shown in the table below.

	1-Day Titration	4-Day Titration	10-Day Titration	Placebo	All Patients
No. randomized	132	132	132	69	465
Did not take study drug	0	2	0	0	2
Lost to follow-up	2	1	0	1	4
Primary analysis group	130	129	132	68	459
Completed	87	92	109	64	352
Discontinued	43	37	23	4	107
Adverse Event	40	34	20	3	94
ineffective	1	2	2	0	5
Intercurrent Illness	0	2	1	0	3
Protocol violation	1	1	0	1	3
Patient Choice	1	1	0	0	2

Demographics

Summary baseline demographic data are shown in the table below. The typical patient was middle-aged to elderly white female with OA of the knee.

The placebo group had a tendency to have more whites and fewer males, but since the more important comparisons are between the active groups, that is not much of an issue. Among the active groups, there was a tendency for the 10-Day group to have a slightly different distribution in sentinel joint, but the overall Chi-squared test of joint and treatment group distribution (restricted to the three active groups) was not statistically significant (p=.19). The only statistically significant difference among active arms, looking at each joint category separately, was for the fraction with spine as sentinel joint (p=.015, by Chi-squared).

Baseline Demographics

	1-Day Titration	4-Day Titration	10-Day Titration	Placebo	All Patients
No. Analyzed	130	129	132	68	459
% Male	37%	28%	30%	25%	29%
% White	90%	89%	89%	97%	90%
Mean Age (years)	62.1	62.3	62.3	61	62
Mean Weight (pounds)	199	193	195	195	796
Sentinel Joint					
Knee	57%	57%	48%	57%	54%
Hip	13%	15%	12%	7.2%	13%
Spine	14%	11%	23%	22%	17%
Other	16%	18%	16%	9%	15%
Mean Time Since Diagnosis (years)	9.6	0.3	8.3	8.1	8.6

Primary Analysis

By protocol, the primary analysis was to be a Cochran-Armitage analysis of linear trend in number of discontinuations due to nausea or vomiting. That analysis and related analyses are shown in the table below:

Primary Analysis of Number of Nausea/Vomiting Discontinuations

	P-value
<u>Cochran-Armitage Test</u>	
Linearity	0.04
Non-Linearity	0.15
<u>Fisher's Exact Test</u>	
<u>Pairwise Comparisons</u>	
1-Day vs. Placebo	0.004
4-Day vs. Placebo	0.009
10-Day vs. Placebo	0.04
1-Day vs. 10-Day	0.15
1-Day vs. 4-Day	0.43
4-Day vs. 10-Day	0.25

(From applicant's Table 10, vol. 57.1, p. 35.)

-Although the primary analysis achieves statistical significance at 0.04 it cannot be interpreted as showing an effect of titration schedule. This is because the linear trend can be explained merely by the difference between placebo and the active arms. The pairwise comparisons, even without adjustment for multiplicity, show no statistically significant differences in discontinuations for nausea or vomiting.

The table below shows the number of nausea/vomiting discontinuations by day for each of the treatment groups, together with total nausea/vomiting discontinuations for each group. An inherent bias in the endpoint definition arises because the more rapid the titration, the longer the exposure at the highest dose, although this bias is partly mitigated by the tendency of these particular adverse events to occur early in treatment. In order to further equalize the comparison, the reviewer computed the numbers of discontinuations for each group before completing 5 days of therapy at 200 mg/day, i.e., considering only discontinuations through day 5 in the 1-Day arm, through day 8 in the 4-Day arm, and through day 14 in the 10-Day arm. This could be viewed as a rate of "failure to achieve target therapy." This endpoint is designated "5D200" in the table.

Discontinuations for Nausea or Vomiting

Day	1-Day Titration		4-Day Titration		10-Day Titration		Placebo	
	Dose	Number	Dose	Number	Dose	Number	Dose	Number
1	200	7	50	2	50		0	
2	200	5	100	3	50	2	0	
3	200	1	150	5	50	2	0	1
4	200	2	200		100		0	
5	200		200		100		0	
6	200		200	1	700	2	0	
7	200	1	200	1	150		0	
8	200		200		150	1	0	
9	200	1	200	1	150	1	0	
10	200		200		200		0	
11	200		200	0	200	1	0	
12	200		200	1	200	1	0	
13	200		200	1	200	1	0	
14	200		200		200		0	
Total ¹		17		15		11		1
5D200 ²		15		12		11		

¹ Total discontinuations: p= 5.45 for difference among the three active arms.

² 5D200=Discontinuations before completing 5 Days at the 200 mg dose: p=0.67 for difference among the three active arms

(Based on applicant's Table 11, vol. 57.1, p. 40. Statistical analyses by reviewer.)

Although there is a slight trend to have fewer discontinuation with slower titration, the study failed to show any statistical, or even clinically very meaningful, difference between titration regimens.

Additional Analyses

The applicant also examined the effect of the titration schedule on discontinuations due to another common symptom grouping, dizziness and/or vertigo. The table below shows discontinuations by day together with an analysis as was done for nausea and vomiting.

Discontinuations for Dizziness or Vertigo

Day	1-Day Titration		4-Day Titration		10-Day Titration		Placebo	
	Dose	Number	Dose	Number	Dose	Number	Dose	Number
1	200	4	50	2	50		0	
2	200	4	100	2	50	1	0	
3	200	2	150	4	50	1	0	
4	200	1	200	1	100		0	
5	200	1	200	2	100		0	
6	200		200	1	100		0	
7	200		200	1	1.50		0	
8	200	1	200		150		0	
9	200	1	200	0	750		0	
10	200		200		200		0	
11	200		200		200		0	
12	200		200		200		0	
13	200		200		200		0	
14	200		200	0	200	0	0	
Total ¹		14		13		2		0
5D200 ²		12		13		2		

¹ Total discontinuations: p= 0.0062 for differences among the three active arms.

² 5D200=Discontinuations before completing 5 Days at the 200 mg dose: p=0.0107 for differences among the three active arms

(Based on applicant's Table 11, vol. 57.1, p. 41. Statistical analyses by reviewer.)

These data indicate that titration schedule has an impact on discontinuations for dizziness and/or vertigo (the large majority of these cases were dizziness) In particular, the 10-Day arm had considerably fewer discontinuations for this adverse event that did the other two arms.

Further investigation showed that one patient in the 10-Day arm was hospitalized for acute dizziness on day 7, and subsequently diagnosed with vestibular neuritis. He was counted as a discontinuation for intercurrent illness, not dizziness. If he were included as a dizziness

discontinuation, the p-value for 5D200 analysis in the above table would change to p=.0269.

Another question has to do with attribution of cause for discontinuation. Based on the applicant's Table 16 (vol. 57.1, p. 54-62) and Attachment 6 (vol. 57.1, p. 113-136), the reviewed tabulated first date of any dizziness or vertigo in any of the patients discontinued for any adverse event. This approach ignored the investigator's attribution of cause and assumes dizziness/vertigo is to blame if the patient ever reported those symptoms. The result of such analysis is show in the table below. (It should be pointed out that in the compilation of these data it was discovered that applicant's Table 16 contained erroneous adverse event entries for subjects requiring reliance on the patient narratives in Attachment 6.)

**Onset of Any Dizziness or Vertigo
in Patients Discontinued for Any Adverse Event**

Day	1-Day Titration		4-Day Titration		10-Day Titration		Placebo	
	Dose	Number	Dose	Number	Dose	Number	Dose	Number
1	200	13	50	4	50	2		0
2	200	7	100	8	50	1		0
3	200	1	150	3	50	3		0
4	200	1	200	2	100			0
5	200		200		100			0
6	200		200	1	100			0
7	200		200		150			0
8	200		200		150			0
9	200		200		150			0
10	200		200		200			0
11	200		200		200	1		0
12	200		200		200			0
13	200		200		200			0
14	200		200		200			0
Total		22		18		7		0
5D200		22		13		7		

¹ Total discontinuations: p= 0.0109 for difference among the three active arms.

² 5D200=Discontinuations before completing 5 Days at the 200 mg dose: p=0.0095 for difference among the three active arms

(Derived from applicant's Table 16, vol. 57.1, p. 54-62 and Attachment 6, p. 113-136.

Statistical analyses by reviewer.)

Even with this alternative attribution, there is fairly strong evidence that titration schedule affects discontinuations due to dizziness/vertigo, with the 10-Day Titration performing best.

The applicant also reported on discontinuations due to any adverse event. The table below presents that data as was done for the other two adverse event groups:

Discontinuations for Any Adverse Event

Day	1-Day Titration		4-Day Titration		10-Day Titration		Placebo	
	Dose	Number	Dose	Number	Dose	Number	Dose	Number
1	200	13	50	2	50		0	
2	200	10	100	7	50	3	0	
3	200	4	150	8	50	3	0	1
4	200	4	200	2	100		0	
5	200	1	200	3	100	1	0	1
6	200	1	200	2	100	2	0	
7	200	2	200	3	150	1	0	
8	200	1	200		150	3	0	
9	200	3	200	1	150	1	0	
10	200		200	1	200	1	0	
11	200	1	200		200	3	0	
12	200		200	1	200	1	0	
13	200		200	1	200	1	0	
14	200		200		200		0	1
Total ¹		40		31		20		3
5D200 ²		32		27		20		

¹ Total discontinuations: $p=0.011$ for difference among the three active arms.

² 5D200=Discontinuations before completing 5 Days at the 200 mg dose: $p=0.157$ for difference among the three active arms

(Based on applicant's Table 11, vol. 57.1, p. 42. Statistical analyses by reviewer.)

A similar trend is seen for all adverse event as was seen for dizziness. However, the relative differences between arms are rendered less dramatic by the addition of numerous events to all three arms. Further, the statistical significance of the differences disappears when one makes allowance (by counting patients only through 5 days of treatment at 200 mg/day, i.e., the 5D200 analysis) for the greater exposures with shorter titrations.

All the analyses above have the defect of not taking into account differential follow-up due to other causes of discontinuation. The applicant therefore also performed lifetable analysis (proportional hazard regression) for discontinuations due to nausea/vomiting, dizziness/vertigo, and any adverse event. Significance levels from those tests are presented below. (These results are quite similar to what was found using Fisher's Exact Test for pairwise comparisons, so the latter results are not presented.)

**Proportional Hazards Regression of
Time to Discontinuation
P-values from Paiwise Comparisons**

Comparison	Nausea and/or Vomiting	Dizziness and/or Vertigo	Any Adverse Event
1 O-Day vs. 1-Day	0.13	<0.001	0.001 -
1 O-Day vs. 4-Day	0.29	0.002	0.05
4-Day vs. 1-Day	0.60	0.71	0.18

{From applicant's Table 12, vol. 57.1, p. 43.}

These results provide fairly strong evidence for superiority of the 10-Day arm over the other two for dizziness/vertigo discontinuations and of the 10-Day arm over the 1-Day arm for any adverse event discontinuations, even if one were to make modest adjustments for multiplicity.

Pain Scores and Global Assessments

The applicant did not provide statistical analysis of efficacy variables, but a tabulation of results was provided:

Pain Score, Globals and Rescue Use

	1-Day Titration	4-Day Titration	1 O-Day Titration	Placebo
<u>Pain Score Change from Baseline</u>				
Mean	-1.3	-1.5	-1.7	-1.1
SD	2.8	2.7	2.9	2.8
N	125	124	130	56
<u>Patient Global</u>				
Very Good	23%	20%	20%	27%
Good	38%	36%	44%	26%
No Change	29%	33%	26%	37%
Poor	2%	5%	5%	9%
Very Poor	5%	4%	4%	6%
Unknown	3%	3%	1%	1%
<u>Patient Global</u>				
Very Good	13%	15%	17%	22%
Good	41%	39%	44%	25%
No Change	31%	33%	30%	41%
Poor	4%	6%	4%	7%
Very Poor	3%	2%	4%	3%
Unknown	4%	5%	1%	2%
<u>Fraction Use rescue</u>				
	11%	9%	9%	7%

{From applicant's Table 19, vol. 57.1, p. 69.}

There was no evident tendency for the slower titration groups to be less effective. In fact the 10-Day arm had a numerically larger fall in pain score and a larger fraction in the Good+Very Good groups for both globals.

Safety

There were no deaths in the double-blind study. Three serious adverse events were reported: cholecystitis in the 1-Day arm, vestibular neuritis in the 10-Day arm, and angina pectoris in the Placebo arm. None was considered related to study drug.

The non-serious adverse events were in line with what is expected of tramadol. There were no significant findings for vital signs or laboratory values.

CONCLUSIONS:

Although a statistically significant p-value was attained for the protocol primary analysis, the study could technically be considered a failed study because the significant finding for the primary endpoint can be attributed to the difference between placebo and active arms and not to the effect of titration schedule.

However, this study is not offered in support of a new indication or for a comparative claim. Therefore it should be viewed not so much as formal hypothesis test but as an exploration. One might argue that some sort of titration could be suggested just on reasonable speculation. To have data from a study in which specific regimens have been tested is that much the better. The applicant should be commended for undertaking such an investigation to improve the knowledge base on how to use this drug. This reviewer feels the data offer sufficiently strong evidence that slow titration can reduce discontinuations, particularly those due to dizziness/vertigo, so as to support adding the proposed wording to the labeling.

While the study used osteoarthritis patients, it is not adequate to provide substantial evidence of efficacy, and should not be used to promote use in osteoarthritis.

RECOMMENDATIONS:

The supplement should be approved, with the understanding that the appeal of the request of 1/30/98 is still under consideration.

Orig NDA # 20-281
HFD-550/Div File
HFD-340
HFD-550/CSO/Gunter
HFD-550/MO/Hyde

|S|

John E. Hyde, Ph.D., M.D.

8-21-98

EXCLUSIVITY SUMMARY for NDA # 20-281 SUPPL # 14

Trade Name ULTRAM Generic Name TRAMADOL

Applicant Name R.W. Johnson HFD- 550

Approval Date, if known 8-21-98

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES / / NO / /

b) Is it an effectiveness supplement?

YES / / NO / /

If yes, what type? (SE1, SE2, etc.) (coded SE1, but

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability, or bioequivalence data, answer "no.")

YES / / NO / /
1500 Comment

Comment: Sponsor did a double-blind, randomized clinical trial to compare initiation of Ultram therapy using a 10-day titration vs. starting therapy at full dose. They showed 10-day titration led to fewer discontinuations for certain adverse events. This resulted in approval of labeling change in

DOSAGE AND ADMINISTRATION to report that starting therapy with a titration ~~method~~ could reduce some discontinuations.

d) Did the applicant request exclusivity?

YES / / NO / /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form strength, route of administration, and dosing previously been approved by FDA for the same use? (Rx-to-OTC switches should be answered NO-please, indicate as such.)

YES / / NO / /

If yes, NDA # _____ Drug Name _____

If the answer to question 2 is "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES / / NO / /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / / NO /

If "yes," identify the approved drug product(s) containing active moiety, and, if known, the NDA #(s). the

NDA# 20-281 ULTRAM
NDA# _____
NDA# _____

2. Combination product

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an ~~application~~ under section SOS containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

N/A YES /___/ NO /___/

if "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____
NDA# _____
NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3 (a). If the answer to 3 (a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

/ See comment on page 1.

Study compared 2 dosing regimens for starting Ultram therapy and showed that slow titration had fewer adverse event discontinuations YES / / NO / /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / / NO / /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE: 8:

YES / / NO / /

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /X/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

12) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /X/

If yes, explain: _____

(c) If the answers to (b) (1) and (b) (2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

#1 = TPS DOS: An Evaluation of Varying Titration Rates of ULTRAM

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES / <input type="checkbox"/> /	NO / <input checked="" type="checkbox"/> /
Investigation #2	YES / <input type="checkbox"/> /	NO / <input type="checkbox"/> /

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES / /	NO / <input checked="" type="checkbox"/> /
Investigation #2	YES / /	NO / <input type="checkbox"/> /

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no., identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

#1 IPS-DOS

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES / X / NO / ___ / Explain: _____

Investigation #2

IND ___ # YES / ___ / NO / ___ / Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES / ___ / Explain: _____ NO / ___ / Explain _____

Investigation #2

YES / ✓ / Explain: _____ NO / ___ / Explain _____

Approved Package for Dosing Schedule

Approved December 23, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for: 020281/S016

Application Number: 020281/S016

Trade Name: ULTRAM 50 AND 100 Mg TABLETS

Generic Name: TRAMADOL HYDROCHLORIDE

Sponsor: R.J. JOHNSON RESEARCH INSTITUTE

Approval Date: 12/23/99

**INDICATION(s): FOR THE MANAGEMENT OF
MODERATE TO MODERATELY SEVERE PAIN**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 020281/S016

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tentative Approval Letter				X
Approvable Letter				X
Printed Labeling	X			
Medical Review(s)	X			
Chemistry Review(s)	X			
EA/FONSI				X
Pharmacology Review(s)				X
Statistical Review(s)				X
Microbiology Review(s)				X
Clinical Pharmacology				X
Biopharmaceutics Review(s)				
Bioequivalence Review(s)				X
Administrative/ Correspondence Document(s)	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 020281/S016

APPROVAL LETTER

NDA 20-281/S-016

The R.W. Johnson Research Institute
Attention: Natasha Rogozenski
Assistant Director of Regulatory Affairs
920 Route 202 South
P.O. Box 300
Raritan, New Jersey 08869-0602

Dear Ms. Rogozenski:

Please refer to your supplemental new drug application dated February 23, 1999, received February 26, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ultram (tramadol hydrochloride tablets) Tablets, 50 mg and 100 mg.

We acknowledge receipt of your submissions dated March 8 and 30; April 16; June 7; August 25; and December 2, 14, and 22, 1999.

This supplemental new drug application provides for the addition of a score to the Ultram 50 mg Tablet in order to allow a titration dosing regimen using a 25 mg dose.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplemental NDA number 20-28 E-016." Approval of this submission by FDA is not required before the labeling is used.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this

NDA 20-281/S-016

Page 2

requirement is waived or deferred (63 FR 66632). We note that you have not fulfilled the

requirements of 21 CFR 314.55 (or 601.27). We are deferring submission of your pediatric studies until 12/02/2000. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505.4 of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity, you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will proceed with the pediatric drug development plan that you submit and notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does in fulfill the requirements of the pediatric rule.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NDA 20-281/S-016

Page 3

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.51

If you have any questions, contact Yoon J. Kong, Pharm.D., Regulatory Project Manager, at (301) 827-2090.

Sincerely,

/s/

Karen Midthun, M.D.
Director

Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

APPEARS THIS WAY
ORIGINAL

Attachment: Labeling

APPEARS THIS WAY

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020281/S016

PRINTED LABELING

1 **ULTRAM[®] (tramadol hydrochloride tablets)**

2 **DESCRIPTION**

3 ULTRAM[®] (tramadol hydrochloride tablets) is a centrally acting
4 analgesic. The chemical name for tramadol hydrochloride is (\pm)*cis*-2-
5 [(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol
6 hydrochloride. Its structural formula is:
7
8

9 [Structural Formula]
10
11

12 The molecular weight of tramadol hydrochloride is 299.8. Tramadol
13 hydrochloride is a white, bitter, crystalline and odorless powder. It is
14 readily soluble in water and ethanol and has a pKa of 9.41. The
15 water/n-octanol partition coefficient is 1.35 at pH 7. ULTRAM tablets
16 contain 50 mg of tramadol hydrochloride and are white in color. Inactive
17 ingredients in the tablet are corn starch, hydroxypropyl methylcellulose,
18 lactose, magnesium stearate, microcrystalline cellulose, polyethylene
19 glycol, polysorbate 80, sodium starch glycolate, titanium dioxide and
20 wax.
21

22 **CLINICAL PHARMACOLOGY**

23 **Pharmacodynamics**

24 ULTRAM is a centrally acting synthetic analgesic compound. Although
25 its mode of action is not completely understood, from animal tests, at
26 least two complementary mechanisms appear applicable: binding of
27 parent and M1 metabolite to μ -opioid receptors and weak inhibition of
28 reuptake of norepinephrine and serotonin. Opioid activity is due to both
29 low affinity binding of the parent compound and higher affinity binding of
30 the O-demethylated metabolite M1 to μ -opioid receptors. In animal
31 models, M1 is up to 6 times more potent than tramadol in producing

32 analgesia and 200 times more potent in μ -opioid binding, Tramadol-
33 induced analgesia is only partially antagonized by the opiate antagonist
34 naltrexone in several animal tests. The relative contribution of both
35 tramadol and M1 to human analgesia is dependent upon the plasma
36 concentrations of each compound (see CLINICAL PHARMACOLOGY,
37 Pharmacokinetics).

38 Tramadol has been shown to inhibit reuptake of norepinephrine and
39 serotonin *in vitro*, as have some other opioid analgesics. These
40 mechanisms may contribute independently to the overall analgesic
41 profile of ULTRAM. Analgesia in humans begins approximately within
42 one hour after administration and reaches a peak in approximately two
43 to three hours.

44 Apart from analgesia, ULTRAM administration may produce a
45 constellation of symptoms (including dizziness, somnolence, nausea,
46 constipation, sweating and pruritus) similar to that of an opioid.

4 7 However, tramadol causes less respiratory depression than morphine
48 at recommended doses (see OVERDOSAGE). In contrast to
49 morphine, tramadol has not been shown to cause histamine release. At
50 therapeutic doses, ULTRAM has no effect on heart rate, left-ventricular
51 function or cardiac index. Orthostatic hypotension has been observed.

52 Pharmacokinetics

53 The analgesic activity of ULTRAM is due to both parent drug and the M1
54 metabolite (see CLINICAL PHARMACOLOGY, Pharmacodynamics).
55 Tramadol is administered as a racemate and both the [-] and [+] forms
56 of both tramadol and M1 are detected in the circulation. Tramadol is
57 well absorbed orally with an absolute bioavailability of 75%. Tramadol
58 has a volume of distribution of approximately 2.7L/kg and is only 20%
59 bound to plasma proteins. Tramadol is extensively metabolized by a
60 number of pathways, including CYP2D6 and CYP3A4, as well as by
61 conjugation of parent and metabolites. One metabolite, M1, is
62 pharmacologically active in animal models, The formation of M1 is

63 dependent upon Cytochrome P-450(2D6) and as such is subject to
64 both metabolic induction and inhibition which may affect the therapeutic
65 response (see PRECAUTIONS - Drug interactions). Tramadol and its
66 metabolites are excreted primarily in the urine with observed plasma
67 half-lives of 6.3 and 7.4 hours for tramadol and M1, respectively. Linear
68 pharmacokinetics have been observed following multiple doses of 50
69 and 100 mg to steady-state.

70 Absorption:

71 Racemic tramadol is rapidly and almost completely absorbed after oral
72 administration. The mean absolute bioavailability of a 100 mg oral dose
73 is approximately 75%. The mean peak plasma concentration of
74 racemic tramadol and M1 occurs at two and three hours, respectively,
75 after administration in healthy adults. In general, both enantiomers of
76 tramadol and M1 follow a parallel time course in the body following
77 single and multiple doses although small differences (- 10%) exist in the
78 absolute amount of each enantiomer present.

79 Steady-state plasma concentrations of both tramadol and M1 are
80 achieved within two days with q.i.d. dosing. There is no evidence of
81 self-induction (see Figure 1 and Table 1 below).

82

83

[Figure 1]

84

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86
87
88

Table 1
Mean (%CV) **Pharmacokinetic** Parameters for
Racemic Tramadol and **M1 Metabolite**

Population/ Dosage Regimen ^a	Parent Drug Metabolite	Peak Conc. (ng/mL)	Time to Peak (hrs)	Clearance/F ^b (mL/min/Kg)	t _{1/2} (hrs)
Healthy Adults, 100 mg qid, MD p.o.	Tramadol	592 (30)	2.3 (61)	5.90 (25)	6.7 (15)
	M1	110 (29)	2.4 (46)	c	7.0 (14)
Healthy Adults, 100 mg SD p.o.	Tramadol	308 (25)	1.6 (63)	8.50 (31)	5.6 (20)
	M1	55.0 (36)	3.0 (51)	c	6.7 (16)
Geriatric. (>75 yrs) 50 mg SD p.o.	Tramadol	208 (31)	2.1 (19)	6.39 (25)	7.0 (23)
	M1	d	d	c	d
Hepatic Impaired; 50 mg SD p.o.	Tramadol	217 (11)	1.9 (15)	4.23 (56)	13.3 (11)
	M1	19.4 (12)	9.8 (20)	c	18.5 (15)
Renal Impaired, CL _r 1 C-30 mL/min 100 mg SD i.v.	Tramadol	c	c	4.23 (54)	10.6 (31)
	M1	c	c	c	11.5 (40)
Renal Impaired, CL _r <5 mL/min 100 mg SD i.v.	Tramadol	c	c	3.73 (17)	11.0 (29)
	M1	c	c	c	16.9 (78)

a9
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9 3
94

- a SD = Single dose. MD = Multiple dose. p.o. = Oral administration,
i.v. = Intravenous administration, q.i.d. = Four times daily
- b F represents the oral bioavailability of tramadol
- c Not applicable
- d Not measured

95 Food *Effects*: Oral administration of ULTRAM with food does not
96 significantly affect its rate or extent of absorption, therefore, ULTRAM
37 can be administered without regard to food.

98 *Distribution*:

99 The volume of distribution of tramadol was 26 and 2.9 liters/kg in male
100 and female subjects, respectively, following a 100 mg intravenous dose.
101 The binding of tramadol to human plasma proteins is approximately
102 20% and binding also appears to be independent of concentration up to
103 10 µg/mL. Saturation of plasma protein binding occurs only at
104 concentrations outside the clinically relevant range. Although not
105 confirmed in humans, tramadol has been shown in rats to cross the
106 blood-brain barrier.

107 *Metabolism*:

108 Tramadol is extensively metabolized after oral administration.
109 Approximately 30% of the dose is excreted in the urine as unchanged
110 drug, whereas 60% of the dose is excreted as metabolites. The
111 remainder is excreted either as unidentified or as unextractable
112 metabolites. The major metabolic pathways appear to be *N*- and *O*-
113 demethylation and glucuronidation or sulfation in the liver. One
114 metabolite (*O*-desmethyltramadol, denoted M1) is pharmacologically
115 active in animal models. Production of M1 is dependent on the CYP2D6
116 isoenzyme of cytochrome P450 and as such is subject to both
117 metabolic induction and inhibition which may affect the therapeutic
118 response (see PRECAUTIONS - Drug Interaction).

119 Approximately 7% of the population has reduced activity of the CYP2D6
120 isoenzyme of cytochrome P-450. These individuals are "poor
121 metabolizers" of debrisoquine, dextromethorphan, tricyclic
122 antidepressants, among other drugs. After a single oral dose of
123 tramadol, concentrations of tramadol were only slightly higher in "poor
124 metabolizers" versus "extensive metabolizers", while M1 concentrations
125 were lower. Concomitant therapy with inhibitors of CYP2D6 such as

126 fluoxetine, paroxetine and quinidine could result in significant drug
127 interactions. In vitro drug interaction studies in human liver microsomes
128 indicate that inhibitors of CYP2D6 such as fluoxetine and its metabolite
129 norfluoxetine, amitriptyline and quinidine inhibit the metabolism of
130 tramadol to various degrees, suggesting that concomitant
131 administration of these compounds could result in increases in tramadol
132 concentrations and decreased concentrations of M1. The
133 pharmacological impact of these alterations in terms of either efficacy
134 or safety is unknown.

135 *Elimination:*

136 The mean terminal plasma elimination half-lives of racemic tramadol
137 and racemic M1 are 6.3 ± 1.4 and 7.4 ± 1.4 hours, respectively. The
138 plasma elimination half-life of racemic tramadol increased from
139 approximately six hours to seven hours upon multiple dosing.

140 **Special Populations**

141 *Renal:*

142 Impaired renal function results in a decreased rate and extent of
143 excretion of tramadol and its active metabolite, M1. In patients with
144 creatinine clearances of less than 30 mL/min, adjustment of the dosing
145 regimen is recommended (see DOSAGE AND ADMINISTRATION).
146 The total amount of tramadol and M1 removed during a 4-hour dialysis
147 period is less than 7% of the administered dose.

148 *Hepatic:*

149 Metabolism of tramadol and M1 is reduced in patients with advanced
150 cirrhosis of the liver, resulting in both a larger area under the
151 concentration time curve for tramadol and longer tramadol and M1
152 elimination half-lives (13 hr. for tramadol and 19 hr. for M1). In cirrhotic
153 patients, adjustment of the dosing regimen is recommended (see
154 DOSAGE AND ADMINISTRATION).

155 Age.

156 Healthy elderly subjects aged 65 to- 75 years have plasma tramadol
157 concentrations and elimination half-lives comparable to those observed
158 in healthy subjects less than 65 years of age. In subjects over 75 years,
159 maximum serum concentrations are slightly elevated (208 vs. 162
160 ng/mL) and the elimination half-life is slightly prolonged (7 vs. 6 hours)
161 compared to subjects 65 to 75 years of age. Adjustment of the daily
162 dose is recommended for patients older than 75 years (see DOSAGE
163 AND ADMINISTRATION).

164 Gender:

165 The absolute bioavailability of tramadol was 73% in males and 79% in
166 females. The plasma clearance was 6.4 mL/min/kg in males and 5.7
167 mL/min/kg in females following a 100 mg IV dose of tramadol.
168 Following a single oral dose, and after adjusting for body weight,
169 females had a 12% higher peak tramadol concentration and a 35%
170 higher area under the concentration-time curve compared to males.
171 The clinical significance of this difference is unknown.

172 Clinical Studies

173 ULTRAM has been given in single oral doses of 50, 75, 100, 150 and
174 200 mg to patients with pain following surgical procedures and pain
175 following oral surgery (extraction of impacted molars).

176 in single-dose models of pain following oral surgery, pain relief was
177 demonstrated in some patients at doses of 50 mg and 75 mg. A dose
178 of 100 mg ULTRAM tended to provide analgesia superior to codeine
179 sulfate 60 mg, but it was not as effective as the combination of aspirin
180 650 mg with codeine phosphate 60 mg. In single-dose models of pain
181 following surgical procedures, 150 mg provided analgesia generally
182 comparable to the combination of acetaminophen 650 mg with
183 propoxyphene napsylate 100 mg, with a tendency toward later peak
184 effect.

185 ULTRAM has been studied in three long-term controlled trials
186 involving a total of 820 patients, with 530 patients receiving ULTRAM.

187 Patients with a variety of chronic painful conditions were studied in
188 double-blind trials of one to three months duration. Average daily doses
189 of approximately 250 mg of ULTRAM in divided doses were generally
190 comparable to five doses of acetaminophen 300 mg with codeine
191 phosphate 30 mg (TYLENOL[®] with Codeine #3) daily, five doses of
192 aspirin 325 mg with codeine phosphate 30 mg daily, or two to three
193 doses of acetaminophen 500 mg with oxycodone hydrochloride 5 mg
194 (TYLOX[®]) daily.

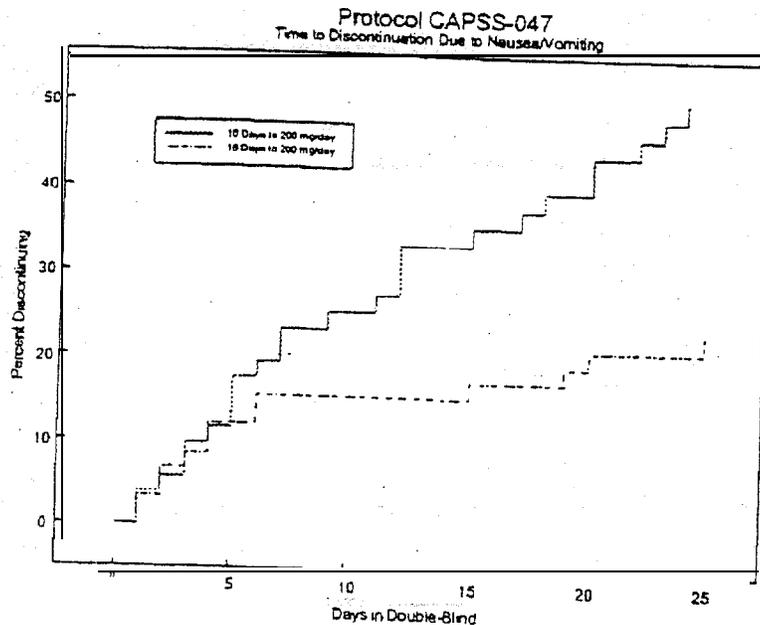
195 **Titration Trials**

196 In a randomized, blinded clinical study with 129 to 132 patients per
197 group, a 10-day titration to a daily ULTRAM dose of 200 mg (50 mg
198 q.i.d.), attained in 50 mg increments every 3 days, was found to result in
199 fewer discontinuations due to dizziness or vertigo than titration over only
200 4 days or no titration. In a second study with 54 to 59 patients per
201 group, patients who had nausea or vomiting when titrated over 4 days
202 were randomized to re-initiate ULTRAM therapy using slower titration
203 rates. A 16-day titration schedule, starting with 25 mg qAM and using
204 additional doses in 25 mg increments every third day to 100 mg/day (25
205 mg q.i.d.), followed by 50 mg increments in the total daily dose every
206 third day to 200 mg/day (50 mg q.i.d.), resulted in fewer
207 discontinuations due to nausea or vomiting and fewer discontinuations
208 due to any cause than did a 10-day titration schedule.

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209

Figure 2



210

211 **INDICATIONS AND USAGE**

212 ULTRAM is indicated for the management of moderate to moderately
213 severe pain.

214

215 **CONTRAINDICATIONS**

216 ULTRAM should not be administered to patients who h&e previously
217 demonstrated hypersensitivity to tramadol, any other component of this
218 product or opioids. It is also contraindicated in cases of acute
219 intoxication with alcohol, hypnotics, centrally acting analgesics, opioids
220 or psychotropic drugs.

221

222 **WARNINGS**

223 **Seizure Risk**

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

- 229 • **serotonin reuptake inhibitors (SSRI**
230 **antidepressants or anorectics),**
- 231 • **Tricyclic antidepressants (TCAs), and other tricyclic**
232 **compounds (e.g., cyclobenzaprine, promethazine, etc.),**
233 **or**
- 234 • **Opioids.**

235 **Administration of ULTRAM may enhance the seizure risk in**
236 **patients taking;**

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

241 **Risk of convulsions may also increase in patients with epilepsy,**
242 **those with a history of seizures, or in patients with a recognized**
243 **risk for seizure (such- as head trauma, metabolic disorders,**
244 **alcohol and drug withdraw+, CNS infections). In ULTRAM**
245 **overdose, naloxone administration may increase the risk of**
246 **seizure.**

247 **Anaphylactoid Reactions**

248 **Serious and rarely fatal anaphylactoid reactions have been reported in**
249 **patients receiving therapy with ULTRAM. These reactions often occur**
250 **following the first dose. Other reported reactions include pruritus, hives,**
251 **bronchospasm, and angioedema. Patients with a history of**
252 **anaphylactoid reactions to codeine and other opioids may be at**

253 increased risk and therefore should not receive ULTRAM (see
254 CONTRAINDICATIONS).

255 **Use in Opioid-dependent Patients**

256 ULTRAM should not be used in opioid-dependent patients. ULTRAM
257 has been shown to reinitiate physical dependence in some patients that
258 have been previously dependent on other opioids. Consequently, in
259 patients with a tendency to opioid abuse or opioid dependence,
260 treatment with ULTRAM is not recommended.

261 **Use with CNS Depressants**

262 ULTRAM should be used with caution and in reduced dosages when
263 administered to patients receiving CNS depressants such as alcohol,
264 opioids, anesthetic agents, phenothiazines, tranquilizers or sedative
265 hypnotics.

266 **Use with MAO Inhibitors**

267 **Use** ULTRAM with **great** caution in patients taking monoamine oxidase
268 inhibitors, because animal studies have shown increased deaths with
269 combined administration.

270

271 **PRECAUTIONS**

272 **Respiratory Depression**

273 Administer ULTRAM cautiously in patients at risk for respiratory
274 depression. When large doses of ULTRAM are administered with
275 anesthetic medications or alcohol, respiratory depression may result.

276 Treat such cases as an overdose. If naloxone is to be administered,
277 use cautiously because it may precipitate seizures (see WARNINGS,
278 Seizure Risk and OVERDOSAGE).

279 **Increased intracranial Pressure or Head Trauma'**

280 ULTRAM should be used with caution in patients with increased
281 intracranial pressure or head injury. Pupillary changes (miosis) from
282 tramadol may obscure the existence, extent, or **course** of intracranial
283 pathology. Clinicians should also maintain a high index of suspicion for

284 adverse drug reaction when evaluating altered mental status in these
285 patients if they are receiving ULTRAM.

286 Acute Abdominal **Conditions**

287 The administration of ULTRAM may complicate the clinical assessment
288 of patients with acute abdominal conditions.

289 **Withdrawal**

290 ~~Withdrawal symptoms may occur if ULTRAM is discontinued abruptly.~~
291 ~~These symptoms may include: anxiety, sweating, insomnia, rigors; pain;~~
292 ~~nausea, tremors, diarrhoea, upper respiratory symptoms, piloerection,~~
293 ~~and rarely hallucinations. Clinical experience suggests that withdrawal~~
294 ~~symptoms may be relieved by tapering the medication.~~

295 **Patients Physically Dependent on Opioids**

296 ULTRAM is not recommended for patients who are dependent on
297 opioids. Patients who have recently taken substantial amounts of
298 opioids may experience withdrawal symptoms. Because of the difficulty
299 in assessing dependence in patients who have previously received
300 substantial amounts of opioid medication, administer ULTRAM
301 cautiously to such patients.

302 **Use in Renal and Hepatic Disease**

303 Impaired renal function results in a decreased rate and extent of
304 excretion of tramadol and its active metabolite, M1. In patients with
305 ~~creatinine clearances of less than 30 mL/min, dosing reduction is~~
306 recommended (see DOSAGE AND ADMINISTRATION).

307 Metabolism of tramadol and M1 is reduced in patients with advanced
308 cirrhosis of the liver. In cirrhotic patients, dosing reduction is
309 recommended (see DOSAGE AND ADMINISTRATION).

310 With the prolonged half-life in these conditions, achievement of steady-
311 state is delayed, so that it may take several days for elevated plasma
312 concentrations to develop.

313 **Information for Patients**

- 314 • ULTRAM (**tramadol** hydrochloride tablets) may impair mental or
- 315 physical abilities required for the performance of potentially
- 316 **hazardous tasks such as driving a car** or operating machinery.
- 317 • ULTRAM should not be taken **with alcohol** containing beverages.
- 318 • ULTRAM should be used **with caution** when taking medications such
- 319 as tranquilizers, hypnotics or other opiate containing analgesics.
- 320 • The patient should be instructed to inform the **physician** if they are
- 321 pregnant, think they might become pregnant, or are trying to become
- 322 pregnant (see PRECAUTIONS: Labor and Delivery).
- 323 • The patient should understand the single-dose and 24-hour dose
- 324 limit and the time interval between doses, since exceeding these
- 325 recommendations can result in respiratory depression and seizures.

326

327 Drug **interactions**

328 Tramadol does not appear to induce its own metabolism in humans,
329 *since observed* maximal plasma concentrations after multiple oral
330 doses are higher than expected based on single-dose data. Tramadol
331 is a mild inducer of selected drug metabolism pathways measured in
332 animals.

333 *Use with Carbamazepine*

334 Concomitant administration of ULTRAM with **carbamazepine**
335 causes a significant increase in tramadol metabolism, presumably
336 through metabolic **induction** by *carbamazepine*. Patients receiving
337 chronic *carbamazepine* doses of up to 800 mg daily may require up to
338 twice the recommended dose of ULTRAM.

339 *Use with Quinidine*

340 Tramadol is metabolized to M1 by the CYP2D6 P-450 isoenzyme.
341 Quinidine is a **selective** inhibitor of that isoenzyme, so that concomitant
342 administration of *quinidine* and ULTRAM results in increased
343 concentrations of tramadol and reduced concentrations of M1. **The**
344 clinical consequences of these findings are unknown. *In vitro*, drug

345 interaction studies in human liver microsomes indicate that tramadol
346 has no effect on quinidine metabolism.

347 Use with *Inhibitors* of CYP2D6

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

352 Use with *Cimetidine*

353 **Concomitant** administration of ULTRAM with **cimetidine** does not
354 result in clinically significant changes in tramadol pharmacokinetics.
355 Therefore, **no alteration** of the ULTRAM dosage **regimen is**
356 recommended.

357 Use with *MAO Inhibitors*

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

361 Use with *Digoxin* and *Warfarin*

362 Post-marketing surveillance has revealed rare reports of digoxin
363 toxicity and alteration of warfarin effect, including elevation of
364 prothrombin times.

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365 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

375 A slight, but statistically significant, increase in two common murine
376 tumors, pulmonary and hepatic, was observed in a mouse
377 carcinogenicity study, particularly in aged mice (dosing orally up to 30
378 mg/kg for approximately two years, although the study was not done with
379 the Maximum Tolerated Dose). This finding is not believed to suggest
380 risk in humans. No such finding occurred in a rat carcinogenicity study.

381 No effects on fertility were observed for tramadol at oral dose levels
382 up to 50 mg/kg in male rats and 75 mg/kg in female rats.

383

384 **Pregnancy. Teratogenic Effects: Pregnancy Category C**

385 There are no adequate and well-controlled studies in pregnant women.
386 ULTRAM should be used during pregnancy only if the potential benefit
387 justifies the potential risk to the fetus.

388 Tramadol has been shown to be embryotoxic and fetotoxic in mice,
389 rats and rabbits at maternally toxic doses 3 to 15 times the maximum
390 human dose or higher (120 mg/kg in mice, 25 mg/kg or higher in rats
391 and 75 mg/kg or higher in rabbits), but was not teratogenic at these
392 dose levels. No harm to the fetus due to tramadol was seen at doses
393 that were not maternally toxic.

394 No drug-related teratogenic effects were observed in progeny of
395 mice, rats or rabbits treated with tramadol by various routes (up to 140

396 mg/kg for mice, 80 mg/kg for rats or 300 mg/kg for rabbits). Embryo
397 and fetal toxicity consisted primarily of decreased fetal weights, skeletal
398 ossification and increased supernumerary ribs at maternally toxic dose
399 levels. Transient delays in developmental or behavioral parameters
400 were also seen in pups from rat dams allowed to deliver. Embryo and
401 fetal lethality were reported only in one rabbit study at 300 mg/kg, a
402 dose that would cause extreme maternal toxicity in the rabbit.

403 In peri- and post-natal studies in rats, progeny of dams receiving oral
404 (gavage) dose levels of 50 mg/kg or greater had decreased weights,
405 and pup survival was decreased early in lactation at 80 mg/kg (6 to 10
406 times the maximum human dose). No toxicity was observed for progeny
407 of dams receiving 8, 10, 20, 25 or 40 mg/kg. Maternal toxicity was
408 observed at all dose levels, but effects on progeny were evident only at
409 higher dose levels where maternal toxicity was more severe.

410 **Labor and Delivery**

411 ULTRAM should not be used in pregnant women prior to or during labor
412 unless the potential benefits outweigh the risks. Safe use in pregnancy
413 has not been established. Chronic use during pregnancy may lead to
414 physical dependence and post-partum withdrawal symptoms in the
415 newborn. Tramadol has been shown to cross the placenta. The mean
416 ratio of serum tramadol in the umbilical veins compared to maternal
417 veins was 0.83 for 40 women given tramadol during labor.

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

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420 **Nursing Mothers**

421 ~~ULTRAM is not recommended~~ for obstetrical preoperative medication
422 or for post-delivery **analgesia in nursing mothers because** its safety in
423 infants and newborns has not been studied. Following a single IV 100
424 mg dose of tramadol, the cumulative excretion in breast milk within 16
425 hours postdose was 100 μg of tramadol (0.1% of the maternal dose)
426 and 27 μg of MI.

427 **Pediatric Use**

428 The pediatric use of ULTRAM is not recommended because safety and
429 efficacy in patients under 16 years of age have not been established.

430 **Use in the Elderly**

431 In subjects over the age of 75 years, serum concentrations are slightly
432 elevated and the elimination half-life is slightly prolonged. The aged
433 also can be expected to vary more widely in their ability to tolerate
434 adverse drug effects. Daily doses in excess of 300 mg are not
435 recommended in patients over 75 (see DOSAGE AND
436 ADMINISTRATION).

437

438 **ADVERSE REACTIONS**

439 **ULTRAM** was administered to 550 patients during the double-blind or
440 open-label extension periods in U.S. studies of chronic nonmalignant
441 pain. Of these patients, 375 were 65 years old or older. Table 2
442 reports the cumulative incidence rate of **adverse** reactions by 7, 30 and
443 90 days for the most frequent reactions (5% or more by 7 days). The
444 most frequently reported events were in the **central nervous** system and
445 gastrointestinal system. Although the reactions listed in the table are felt
446 to be probably related to ULTRAM administration, the reported rates
447 also include some events that may have been due to underlying disease
448 or concomitant medication. The overall incidence rates of adverse
449 experiences in these trials were similar for ULTRAM and the active
450 control groups, **TYLENOL**® with Codeine #3 (acetaminophen 300 mg

451 with codeine phosphate 30 mg), and aspirin 325 mg with codeine
452 phosphate 30 mg.

453

454

455

456

Table 2
Cumulative Incidence of Adverse Reactions for ULTRAM in
Chronic Trials of Nonmalignant Pain. (N=427)

	Up to 7 Days	Up to 30 Days	Up to 90 Days
Dizziness/Vertigo	26%	31%	33%
Nausea	24%	34%	40%
Constipation	24%	38%	46%
Headache	18%	26%	32%
Somnolence	16%	23%	25%
Vomiting	9%	13%	17%
Pruritus	8%	10%	11%
"CNS Stimulation"	7%	11%	14%
Asthenia	6%	11%	12%
Sweating	6%	7%	9%
Dyspepsia	5%	9%	13%
Dry Mouth	5%	9%	10%
Diarrhea	5%	6%	10%

457

458 ¹ "CNS Stimulation" is a composite of nervousness, anxiety, agitation,
459 tremor, spasticity, euphoria, emotional lability and hallucinations.

460

461 *Incidence 1% to less than 5%, possibly causally related:* the following
462 lists adverse reactions that occurred with an incidence of 1% to less
463 than 5% in clinical trials, and for which the possibility of a causal
464 relationship with ULTRAM exists.

465

Body as a Whole: Malaise.

466

Cardiovascular: Vasodilation.

467 **Central Nervous System:** Anxiety, Confusion, Coordination
468 disturbance, Euphoria, Nervousness, Sleep disorder.
469 **Gastrointestinal:** Abdominal pain, Anorexia, Flatulence.
470 **Musculoskeletal:** Hypertonia.
471 **Skin:** Rash.
472 **Special Senses:** Visual disturbance.
473 **Urogenital:** Menopausal symptoms, Urinary frequency, Urinary
474 retention.
475
476 Incidence *less than 1%, possibly* causally related: the following lists
477 adverse reactions that occurred with an incidence of less than 1% in
478 clinical trials and/or reported **in** post-marketing experience.
479 Body as a Whole: Accidental injury, Allergic reaction, Anaphylaxis,
480 Suicidal tendency, Weight loss.
481 **Cardiovascular:** Orthostatic hypotension, Syncope, Tachycardia.
482 **Central Nervous System:** Abnormal gait, Amnesia, Cognitive
483 dysfunction. Depression, Difficulty in concentration, Hallucinations,
484 Paresthesia, Seizure (see WARNINGS), Tremor.
485 **Respiratory:** Dyspnea.
486 **Skin:** Stevens-Johnson syndrome/Toxic epidermal necrolysis,
487 Urticaria, Vesicles.
488 **Special Senses:** Dysgeusia.
409 **Urogenital:** Dysuria, Menstrual disorder.
490
491 *Other adverse experiences, causal relationship unknown:* A variety of
492 other adverse events were reported infrequently in patients taking
493 ULTRAM during clinical trials and/or reported in post-marketing
494 experience. A causal relationship between ULTRAM and these events
495 has not been determined. However, the most significant events are
496 listed below as alerting information to the physician.
497 **Cardiovascular:** Abnormal ECG, Hypertension, Hypotension,,

498 Myocardial ischemia, Palpitations
499 Central Nervous System: Migraine, Speech disorders.
500 **Gastrointestinal:** Gastrointestinal bleeding, Hepatitis, Stomatitis.
501 **Laboratory Abnormalities:** Creatinine increase, Elevated liver
502 enzymes, Hemoglobin decrease, Proteinuria.
503 Sensory: Cataracts, Deafness, Tinnitus.

504
505

DRUG ABUSE AND DEPENDENCE

506 ULTRAM has a potential to cause psychic and physical dependence of
507 the morphine-type (μ -opioid). The drug has been associated with
508 craving, drug-seeking behavior and tolerance development. Cases of
509 abuse and dependence on ULTRAM have been reported. ULTRAM
510 should not be used in opioid-dependent patients. ULTRAM can
511 reinstate physical dependence in patients that have been previously
512 dependent or chronically using other opioids. In patients with a
513 tendency to drug abuse, a history of drug dependence, or are
514 chronically using opioids, treatment with ULTRAM is not recommended.

515

OVERDOSAGE

517 Cases of overdose with tramadol have been reported. Estimates of
518 ingested dose in foreign fatalities have been in the range of 3 to 5 g. A
519 3 g intentional overdose by a patient in the clinical studies produced
520 emesis and no sequelae. The lowest dose reported to be associated
521 with fatality was possibly between 500 and 1000 mg in a 40 kg woman,
522 but details of the case are not completely known.

523 Serious potential consequences of overdosage are respiratory
524 depression and seizure. In treating an overdose, primary attention
525 should be given to maintaining adequate ventilation along with general
526 supportive treatment. While naloxone will reverse some, but not all,
527 symptoms caused by overdosage with ULTRAM the risk of seizures is
528 also increased with naloxone administration. In animals convulsions

529 following the administration of toxic doses of tramadol could be
530 suppressed with barbiturates or benzodiazepines but were increased
531 with naloxone. **Naloxone administration** did not change the lethality of
532 an overdose in mice. Hemodialysis is not expected to be helpful in an
533 overdose because it removes less than 7% of the administered dose in
534 a 4-hour **dialysis** period.

535

536

DOSAGE AND ADMINISTRATION

537 For patients with moderate to moderately severe chronic pain not
538 requiring rapid onset of analgesic effect, the tolerability of ULTRAM can
539 be improved by initiating therapy with the following titration regimen:
540 ULTRAM should be started at 25 mg/day qAM and titrated in 25 mg
541 increments **as** separate doses every 3 days to reach 100 mg/day (25
542 mg q.i.d.). Thereafter the total daily dose may be increased by 50 mg
543 as tolerated every 3 days to reach 200 mg/day (50 mg q.i.d.). After
544 titration, ULTRAM 50 to 100 mg can be administered' as needed for
545 pain relief every 4 **to** 6 hours **not to exceed** 400 mg/day.

546

547 For the subset of patients for whom rapid onset of analgesic effect is
548 required and for whom the benefits outweigh the risk of discontinuation
549 due to adverse events associated with higher initial doses, ULTRAM 50
550 mg to 100 mg can be administered as needed for pain relief every four
551 to six hours, **not to exceed** 400 mg per day.

552

553

Individualization of Dose

5 5 4 Available data do not suggest that a dosage adjustment is necessary in
555 elderly patients 65 to 75 years of age unless they also have **renal** or
556 hepatic impairment. For elderly patients **over** 75 years old, not more
557 than 300 mg/day in divided doses as above is recommended. In all
558 patients with **creatinine clearance** less **than** 30 mL/min, it is
559 recommended that the dosing interval of ULTRAM be increased to 12

560 hours, with a maximum daily dose of 200 mg. Since only 7% of an
561 administered dose is removed by, hemodialysis, dialysis patients can
562 receive their regular dose on the day of dialysis. The recommended
563 dose for patients with cirrhosis is 50 mg every 12 hours. Patients
564 receiving chronic carbamazepine doses up to 800 mg daily may
565 require up to twice the recommended dose of ULTRAM.

566
567

568 HOW SUPPLIED

569 ULTRAM (tramadol hydrochloride tablets) Tablets - 50 mg (white,
570 scored, film-coated capsule-shaped tablet) debossed "ULTRAM" on
571 one side and "06 59" on the other side.

572 100's NDC 0045-0659-60 bottles of 100 tablets

573 500's NDC 0045-0659-70 bottles of 500 tablets

574 packages of 100 unit doses in blister packs - NDC 0045-0659-10 (10
575 cards of 10 tablets each).

576

577 Dispense in a tight container. Store at controlled room temperature (up
578 to 25°C, 77°F).

579

580

581 <space allocated for. Ortho-McNeil logo>

582

583

584 **ORTHO-McNEIL**

585 **PHARMACEUTICAL, INC.**

586 Raritan, New Jersey 08869

587

588 U.S. Patents 3,652,589 and 3,830,934

589 © OMP 1998 Revised December 1999 635-10-225-X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATIONNUMBER:020281/S01 6

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW
ANTI-INFLAMMATORY, ANALGESIC AND OPHTHALMIC DRUG
PRODUCTS DMSJON-HFD-550

NDA #: 20,281
SUBMISSION DATE: 20,161, SLR-016
TYPE: February 23, 1999
REVIEW DATE: Labeling Supplement
REVIEWER: July 1, 1999
Mordechai Averbuch, MD

PRODUCT: Ultram® (tramadol hydrochloride)
SPONSOR: R.W. Johnson
920 Route 202
P.O. Box 300
Raritan, NJ 08869
Phone (908) 704-4600

PHARMACOLOGICAL CATEGORY: Analgesic
PROPOSED INDICATIONS: Management of pain
DOSAGE FORM & ROUTE: Scored oral tablets, 50 mg

c s o : c. Lewin

RESUME:

Background

Tramadol hydrochloride is a synthetic, centrally-acting analgesic. The drug has opioid activity and it also inhibits the reuptake of norepinephrine and serotonin. Like opioids, the most frequently reported adverse events are seen in the CNS and GI system to include dizziness/vertigo, headache, somnolence, constipation, nausea, and vomiting. Dizziness/vertigo, nausea and vomiting are events most commonly associated with discontinuation of treatment. With opioids these symptoms usually resolve on continued therapy (except for the constipation) and therefore it is reasonable to investigate strategies to overcome these adverse events at the beginning of therapy. In a previous supplement approved August 1998, the sponsor submitted the results of a study showing that a slow titration to 200 mg/day over 10 days could reduce discontinuation due to adverse events, particularly dizziness and/or vertigo, in comparison to a one or four day titration to 200 mg. As a result, the following paragraph was added to the DOSAGE AND ADMINISTRATION section:

[Redacted]

In the current submission, the sponsor reports the result of a clinical trial designed to determine whether even a slower titration rate of tramadol would reduce the incidence of discontinuation due to nausea and/or vomiting in subjects who previously had difficulty tolerating tramadol because of nausea and/or vomiting. As a result, the applicant proposes to amend the DOSAGE AND ADMINISTRATION section as follows:

[Redacted]

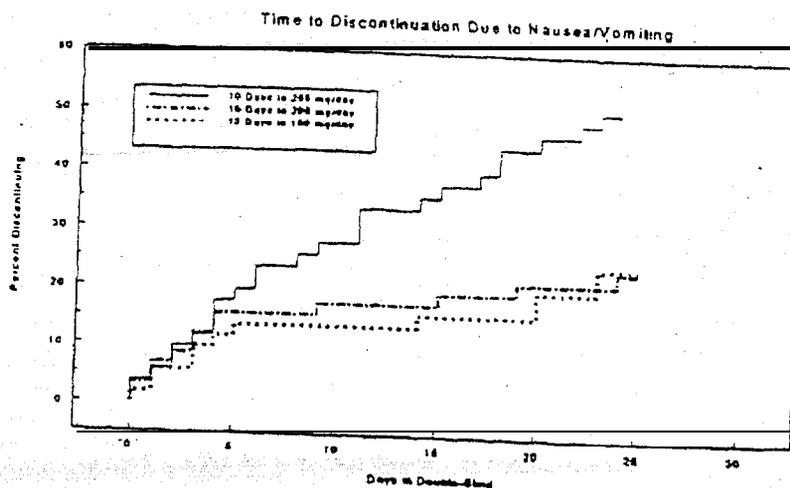
The applicant also proposes to add to the CLINICAL STUDIES section the following information (there is no titration studies' text in the current labeling):

[Redacted]

and/or vomiting and other adverse events was investigated in a clinical trial with two phases, a 14-day open-label run-in and a 28-day double-blind. During the open-label run-in phase subjects were titrated in 50-mg/day increments to a dose of 200 mg/day over four days. Subjects who discontinued tramadol due to nausea and/or vomiting were then eligible to enter the 28-day double-blind phase in which they were randomized to one of three titration regimens. The regimens were: 10-day titration using 50-mg increments every three days to 200 mg/day; 16-day titration using 25-mg increments every three days to 100 mg/day and followed by 50-mg increments every three days to 200 mg/day; 13-day titration using 25-mg increments every three days to 100 mg/day followed by a 50-mg increment for three days to 150 mg/day.

Of 931 subjects with chronic pain who entered the open-label phase, 212 discontinued due to nausea and/or vomiting. Fifty-four, 59, and 54 patients were randomized to the 10-, 16-, and 13-day titration groups respectively. Significantly fewer subjects (22%) discontinued because of nausea and/or vomiting in the 16-day group compared to the 10-day group (46.3%); $p=0.006$ (see Figure 2). Significantly fewer subjects discontinued due to any adverse event in the 16day group (33.9%) vs. the 10-day group (53.7%), $p=0.034$. Results in the 13-day group were similar to the 16day group

Figure 2



BEST POSSIBLE COPY

Clinical Study

Study Design

Overview Of Study Design

This was a multicenter, outpatient, randomized, double-blind, parallel study composed of two phases: a screening/open-label run-in and a double-blind phase. Potential study subjects who had chronic pain for at least three months prior to the study, who received a daily dose of nonsteroidal anti-inflammatory medication (NSAID) for at least 30 days and who required additional pain relief were to be enrolled in the open-label/run-in phase. The open-label/run-in phase was to have been up to 14 days in duration.

In the open-label/run-in phase, tramadol was to be titrated in .50 mg/day increments to 200 mg/day over four days. Subjects were to continue on the 200 mg/day dosage for up to 10 days. Subjects who experienced nausea and/or vomiting during the open-label/run-in phase, severe enough for the subject to discontinue tramadol, were to be randomized into the double-blind phase after a 10-day wash-out period. Approximately 150 adult male and female subjects were to be randomized in the double-blind phase to one of three tramadol treatment regimens. The three tramadol dosage regimens were designed to achieve a maximum dose (200 mg/day or 1.50 mg/day) at different rates of titration (10-, 16- or 13-day). ~~No placebo treatment arm was included in the study.~~ The double-blind phase was to have been up to 28 days in duration. Subjects who did not experience nausea and/or vomiting severe enough to discontinue tramadol by the end of the open-label/run-in phase, were to be discontinued from the study.

E l i

Men and women, 18 years of age or older, who had a chronic painful condition for at least three months prior to study entry not resulting from malignancy and who were otherwise in generally good health, were eligible for enrollment. Eligible subjects must have been on an NSAID daily for at least 30 days prior to the study and required additional pain relief. Women were required to be postmenopausal for at least one year, surgically sterile, or using an adequate form of birth control. Women of childbearing potential were required to have had a negative urine pregnancy test at Visit 1 before open-label study medication was dispensed.

Exclusions

- ❖ Trigeminal neuralgia, post-herpetic neuralgia, a chronic painful condition resulting from malignancy, a painful condition not appropriately treated with chronically administered analgesia (e.g., myocardial infarction, temporomandibular joint syndrome, thrombophlebitis), or a chronic painful condition solely related to dysmenorrhea or recurrent headache
- ❖ A painful condition that required the continued use of analgesic drugs more powerful than study medication.
- ❖ History of estimated creatinine clearance <30 mL/min
- ❖ Abnormal renal or hepatic function that would compromise their welfare or confound the study results.

- Any disease or condition that could result in altered absorption, excess accumulation, or impaired metabolism or excretion of the test medication.
- Subjects who in the opinion of the investigator should not have been enrolled in the study because of the precautions, warnings or contraindications sections of the ULTRAM package insert.
- Investigational drug or investigational device use within the last 30 days.
- Daily opioids use for pain relief.
- History of narcotic abuse or alcohol abuse within the last 12 months.
- Pregnant or lactating women.

Treatment Plan

I. Open-Label Phase

During the open-label phase, all subjects were to receive up to four 50-mg tablets of tramadol daily. Subjects were to titrate according to the following schedule:

- Day 1: 50 mg (AM)
- Day 2: 50 mg b.i.d.
- Day 3: 50 mg t.i.d.
- Days 4-14: 50 mg q.i.d.

2. Double-Blind Phase

Subjects who entered the double-blind phase were assigned randomly to receive one of three tramadol dosage regimens that employed either a 10-, 16-, or 13-day titration schedule in order to achieve a maximum dose of either 200 mg/day for the 10- and 16-day regimens or 150 mg/day for the 13-day regimen. Study medication was administered as two identically-appearing capsules, four times daily (q.i.d.) of either placebo or 25 mg tramadol over the 28-day treatment period (Days 1-28). No placebo treatment arm was included in the study. See table below.

Study Medication Dosage and Titration Schedules During the Double-Blind Phase

Treatment Group (Protocol Regimen #)	Dose of Tramadol HCl by Study Days					
	1-3	4-6	7-9	10-12	13-15	16-28
10-Days to 200 mg (Regimen #1)	50 mg (AM)	50 mg b.i.d.	50 mg t.i.d.	50 mg q.i.d.	50 mg q.i.d.	50 mg q.i.d.
16-Days to 200 mg (Regimen #2)	25 mg (AM)	25 mg b.i.d.	25 mg q.i.d.	25 mg q.i.d.	50 mg t.i.d.	50 mg q.i.d.
13-Days to 150 mg (Regimen #3)	25 mg (AM)	25 mg b.i.d.	25 mg t.i.d.	25 mg q.i.d.	50 mg t.i.d.	50 mg t.i.d.

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Tramadol HCl, 50 mg (Batches R6696, R6968 and R6970) was supplied as tablets in open-label bottles of 100. Tramadol HCl, 25 mg and placebo (Batches R6722, R6723, R6724 and R6725) were supplied as identically-appearing blue opaque, size #0 capsules for the double blind phase.

Concomitant Therapy

No treatment other than the study drug and the subject's stable dose of NSAID were to be used by subjects during the course of the study. However, subjects may have had concurrent illnesses that required prescription or over-the-counter medication during the course of the study. In this event, an accurate record was documented in the case report form of all medications and treatments used during the course of the study, including the drug name, dose, dosage regimen, duration, and indication for such use. In cases where the use of concurrent medication was unavoidable, the investigator made a clinical judgment as to the severity and relatedness of the indication for concurrent medication on the appropriate case report form.

Discontinuations

Subjects could be discontinued from the study due to a serious or limiting adverse event, treatment failure, significant protocol violation (e.g., non-compliance), development of an intercurrent illness that put the subject at undue risk or would have invalidated the study results, or at the request of the subject. Subjects who discontinued were not replaced. At the time of premature withdrawal from the study, efficacy and safety evaluations scheduled for the final visit were to be performed. The investigator was to record the reason for premature discontinuation on the subject's CRF.

Safety Assessment

Safety was evaluated by adverse event monitoring, and by physical examinations, vital signs (sitting blood pressure and pulse rate) and body weight that were measured and recorded at the screening visit, prior to randomization (if applicable), and at the final visit or the day of premature discontinuation.

Efficacy Evaluations

A 10-cm Pain Visual Analogue (VA) scale was used as a pain assessment instrument. PVA assessments were made at the beginning of the open-label/run-in phase and double-blind phase (if applicable) and at final visit or at the time of premature discontinuation. Also, At the final visit or at the time of premature discontinuation, the subjects and the investigators provided an overall rating of how well the study medication controlled the subject's chronic pain. Overall medication assessments utilized a five-point scale with rating ranging from very good to very poor.

Statistical Analysis Planned

Analyses were to be performed for subjects who were randomized to double-blind treatment and took at least one dose of the study medication (i.e., the intent-to-treat group). The primary endpoint of the study was the proportion of subjects in the 10-day and 16-day treatment groups who discontinued study therapy due to nausea and/or vomiting. Pairwise differences between treatments in percent of subjects discontinuing

were to be examined using the chi-square test and the Cochran-Armitage trend test for proportions was to be used to test the hypothesis that slower titration schedules would result in smaller proportions of subjects discontinuing due to nausea and/or vomiting.

The time to discontinuation was also summarized and analyzed for subjects who discontinued due to nausea and/or vomiting. For these analyses, subjects who discontinued study therapy for reasons other than nausea and/or vomiting and subjects who did not discontinue from the study prematurely were treated as censored observations. The distribution of time to discontinuation due to nausea and/or vomiting was summarized for each treatment group. Estimates of the survival distribution for each treatment group were calculated by the Kaplan-Meier method. Differences between treatments were tested using the log-rank test.

The analyses described above for the primary endpoint were repeated for the following secondary endpoints: discontinuations due to any adverse event, discontinuations due to any adverse event/drug ineffective, and discontinuations due to any specific adverse event(s) (other than nausea and/or vomiting) that accounted for a substantial proportion of discontinuations.

Other parameters, including demographic and baseline characteristics, study medication compliance, assessments of pain and efficacy of the study medication, adverse events, vital signs, and body weight measurements, were summarized by double-blind phase treatment group; no analyses were to be performed for these variables.

No statistical tests were planned to evaluate efficacy differences among treatment groups. The mean, median and SD of the PVA scores for both the baseline (end of open-label/run-in phase for those subjects randomized to the double-blind phase) and final visit (or time of discontinuation) were to be calculated and summarized for subjects in the open-label/run-in phase (randomized, non-randomized and all subjects) and double-blind phase (each treatment group).

For the overall medication assessment by the subjects and the investigators, the number and percent of responses in each category (i.e., very good, good, no change, poor and very poor) were tabulated for subjects in the open-label/run-in phase (randomized, non-randomized and all subjects) and double-blind phase (each treatment group).

Analyses Performed

All planned analyses were performed.

In addition, the same analyses were repeated for subjects who discontinued due to headache and dizziness, the only specific adverse events (other than nausea and/or vomiting) that accounted for a substantial proportion of discontinuations. The analysis of the endpoint discontinuation due to all causes was not performed since only four additional subjects discontinued the double-blind phase due to reasons other than adverse events or lack of effectiveness.

Deaths or Discontinuations

I. Open-Label/Run-In Phase

No deaths occurred during the open-label/run-in phase of the study. A total of 301 (32.3%) subjects discontinued open-label treatment due to adverse events (table below). Of these 301 subjects, 166 were randomized to the double-blind phase of the study.

Treatment Limiting Adverse Events Reported by >1% of Open-Label/Run-In Phase Subjects

Adverse Event ^a	Non-Randomized (N=762)		Randomized (N=166)		All Subjects (N=928)	
	n	(% ^b)	n	(% ^b)	n	(% ^b)
Nausea	40	(5.5)	143	(86.1)	185	(20.0)
Vomiting		(2.5)	48	(28.9)	67	(7.2)
Dizziness	34	(4.5)	3	(1.8)	37	(4.0)
Somnolence	41	(2.8)	3	(1.8)	24	(2.6)
Pruritus		(1.7)	0	(0.0)	13	(1.4)
Constipation	8	(1.0)	3	(1.8)	11	(1.2)
Headache	8	(1.0)	3	(1.8)	11	(1.2)
Any Adverse Event	135	(17.7)	166	(100.0)	301	(32.4)

^a Subjects who discontinued because of more than ONE adverse event are included in each category that applies.

^b Percentages are based on the total number of subjects in each group

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2. Double-Blind Phase

No deaths occurred during the double-blind phase of the study. A total of 65 subjects--including 29 (53.7%) in the 10-day, 20 (33.9%) in the 16-day, and 16 (29.5%) in the 13-day tramadol HCl titration groups--discontinued double-blind treatment due to adverse events (table below). Nausea, vomiting, and headache were the adverse events that led to the discontinuation of the greatest numbers of subjects.

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Double-Blind Treatment Limiting Adverse Events Summarized by Treatment Group

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Adverse Event ^a	Tramadol HCl Group/Titration Schedule					
	10-Days to 200 mg/day (N = 54)		16-Days to 200 mg/day (N = 59)		13-Days to 150 mg/day (N = 54)	
	n	(% ^b)	n	(% ^b)	n	(% ^b)
Nausea	25	(42.6)	11	(18.6)	11	(20.4)
Vomiting	4	(7.4)	5	(8.5)	3	(5.6)
Headache				(5.1)	1	(1.9)
Dizziness	2	(3.7)	1	(1.7)	1	(1.9)
Abdominal Pain	2	(3.7)	0	(0.0)	0	(0.0)
Constipation	1	(1.9)	0	(0.0)	1	(1.9)
Rash	0	(0.0)	1	(1.7)	1	(1.9)
Dyspnoea	1	(1.9)	1	(1.7)	0	(0.0)
Gastroesophageal Reflux	1	(1.9)	0	(0.0)	0	(0.0)
Urticaria Abnormal	1	(1.9)	0	(0.0)	0	(0.0)
Depression	1	(1.9)	0	(0.0)	0	(0.0)
Diarrhoea	0	(0.0)	1	(1.7)	0	(0.0)
Mouth Dry	0	(0.0)	1	(1.7)	0	(0.0)
Skeletal Pain	0	(0.0)	0	(0.0)	1	(1.9)
Any Adverse Event	29	(53.7)	20	(33.9)	16	(29.6)

^a Subjects who discontinued because of more than one adverse event are included in each category that applies.

^b Percentages are based on the total number of subjects in each treatment group.

Serious Adverse Events:

Serious adverse events were reported for three subjects, all in the open-label/run-in phase of the study, including Subject 06002 (pain, bronchitis, and COPD), Subject 24018 (squamous cell carcinoma), and Subject 28048 (marked urinary retention secondary to benign prostatic hypertrophy). All of these events were considered by the investigators to have an unlikely relationship to the study medication.

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Efficacy Results

1. Open-Label/Run-In Phase

As shown in the table below, the mean PVA at baseline was 6.0 cm, while the mean PVA at the final open-label visit was 3.3 cm. Over 65% of subjects in the open-label/run-in phase rated the study medication as very good or good. Over 65% of the investigators rated the overall therapeutic effect of the open-label study medication on the subject's pain control as very good or good.

Open-Label/Run-In Efficacy Variables

	Non-Randomized	Randomized	All Subjects
<u>Pain</u>			
Screening			
Mean	5.9 (6.2)	6.2 (6.5)	6.0 (6.2)
(Median)			
Std. Dev.	2.02	1.93	2.01
Min/Max	0.2 /10.0	1.3 /9.8	0.2 /10.0
N	760	167	927
Final OL			
Mean	3.9 (3.6)		3.9 (3.6)
(Median)			
Std. Dev.	2.53		2.53
Min/Max	0.0 /10.0		0.0 /10.0
N	701		701
<u>Subject Overall Assessment</u>			
Missing	N (%)	59 (7.7)	
Very Good	N (%)	205 (26.9)	
Good	N (%)	297 (39.0)	
No Change	N (%)	156 (20.5)	
Poor	N (%)	25 (3.3)	
Very Poor	N (%)	20 (2.6)	
N		762	
<u>Investigator Overall Assessment</u>			
Missing	N (%)	60 (7.9)	
Very Good	N (%)	185 (24.3)	
Good	N (%)	314 (41.2)	
No Change	N (%)	157 (20.6)	
Poor	N (%)	29 (3.8)	
Very Poor	N (%)	17 (2.2)	
N		762	

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2. Double-Blind Phase

As shown in the table below, the mean PVA at the start of the double-blind phase ranged from 5.6 to 6.2 cm among the three tramadol HCl titration groups, while the mean PVA at the final double-blind visit ranged from 4.0 to 4.8 cm.

Over 61% of subjects in each of the three titration groups rated the study medication as very good or good. Over 59% of the investigators rated the overall therapeutic effect of the double-blind study medication on the subject's pain control as very good or good.

Double-Blind Efficacy Variables

	Tramadol HCl Group/Titration Schedule			
	10-Days to 200 mg/day	16-Days to 200 mg/day	13-Days to 150 mg/day	
PVA Pain (cm)				
Baseline ¹				
Mean (Median)	6.2 (6.6)	5.8 (6.5)	5.6 (5.8)	
Std. Dev.	0.35	2.34	2.37	
Min/Max				
N	53 /9.6	0.5 /10.0	0.9 /9.5	
		59	54	
Final				
Mean (Median)	4.8 (5.0)	4.3 (3.5)	4.0 (3.0)	
Std. Dev.	2.70	2.80	2.90	
Min/Max				
N	0.0 /9.9	0.3 /10.0	0.1 /10.0	
	53	59	53	
Subject Overall Assessment				
Missing	N (%)	0 (0.0)	0 (0.0)	1 (1.9)
Very Good	N (%)	13 (24.1)	19 (32.2)	12 (22.2)
Good	N (%)	21 (38.9)	20 (33.9)	21 (38.9)
No Change	N (%)	14 (25.9)	16 (27.1)	16 (29.6)
Poor	N (%)	3 (5.6)	2 (3.4)	2 (3.7)
Very Poor	N (%)	3 (5.6)	2 (3.4)	2 (3.7)
N		54	59	54
Investigator Overall Assessment				
Missing	N (%)	0 (0.0)	17 (28.8)	1 (1.9)
Very Good	N (%)	9 (16.7)	23 (39.0)	9 (16.7)
Good	N (%)	25 (46.3)	14 (23.7)	23 (42.6)
No Change	N (%)	16 (29.6)	5 (8.5)	16 (29.6)
Poor	N (%)	4 (7.4)	5 (8.5)	5 (9.3)
Very Poor	N (%)	0 (0.0)	3 (5.0)	0 (0.0)
N		54	59	54

¹ Start of double-blind phase (Visit 2)

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DISCUSSION:

In a previous supplement approved August 1998, the sponsor presented results of less discontinuations due to dizziness/vertigo when using a 1 C-day titration schedule. This 10-day titration plan did not show significant fewer discontinuations due to nausea/vomiting. In the current submission the sponsor tested a 16-day titration rate in comparison to the approved 1 O-day titration schedule in the aim of achieving less withdrawals due to adverse events. A 13-day titration arm of up to 150 mg of tramadol per day was also included in the study but this reviewer does not find this titration schedule clinically applicable (and apparently so does the sponsor who makes no claim for this titration schedule).

This study is not offered in-support of a new indication or for a comparative claim.

The results of this study indicate that a 16-day titration rate of tramadol does reduce the incidence of discontinuation due to nausea and/or vomiting in subjects who previously had difficulty tolerating tramadol because of nausea and/or vomiting. The percentage of subjects in each double-blind treatment group who discontinued due to nausea and vomiting significantly higher for subjects in the 10-day titration group (46.3% of subjects), than in the 1 S-day and 13-day titration groups (approximately 22% in both).

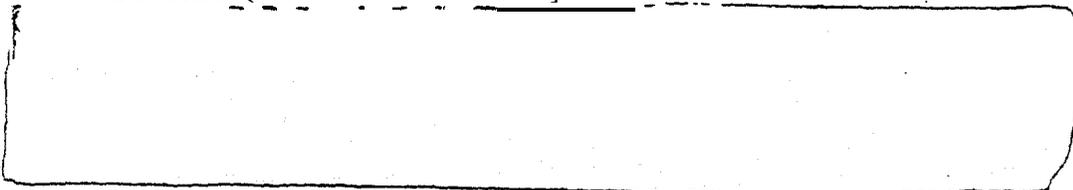
CONCLUSIONS:

This reviewer's opinion is that the data offer sufficiently strong evidence that a 1d-day titration rate can reduce discontinuations due to nausea/vomiting so as to support adding this information to the labeling.

However, this reviewer believes that the proposed wording may miss the target audience. In general, the proposed additions are much too long and detailed than the health care professional may ever need. Moreover, due to this reason, many of them may discontinue reading or may fail to initiate reading the label at all. Also, the 10-day titration schedule is not recommended anymore under the proposed DOSAGE AND ADMINISTRATION section and therefore, there is no apparent reason to provide details of this regimen under the CLINICAL STUDIES section. Below is the proposed sponsor's labeling annotated with this reviewer's comments.

Recommended additions to the proposed package insert are identified by shaded italic and recommended deletions are identified by a single strikethrough line.

Titration Trials (under Clinical Studies)



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DRAFT LABELING

Reviewer's Comments:

The 10-day titration schedule is not recommended anymore under the proposed DOSAGE AND ADMINISTRATION section and therefore, there is no apparent reason to provide details of this regimen under the CLINICAL STUDIES section. Moreover, adding this not-recommended information may create a significant confusion among readers.

DRAFT LABELING

Reviewer's Comments:

Non contributing wording.

DRAFT LABELING

DRAFT LABELING

DOSAGE AND ADMINISTRATION

DRAFT LABELING

Reviewer's Comments: *No comments for this section of the labeling.*

RECOMMENDATIONS:

The supplement should be approved with the above changes in the proposed labeling.

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Supp. NDA # 20,281/016
HFD-550/Div File
HFD-550/CSO/*Kevin Kong*
HFD-550/MO/Averbuch/Hyde
HFD-850/Sta/Lin

/S/ *7/1/99*
M. Averbuch, MD

See also Team leader memo

/S/ *9-18-99*
John E. Hyde, PhD, MD

MEDICAL TEAM LEADER REVIEW

ANTI-INFLAMMATORY, ANALGESIC AND OPHTHALMIC DRUG
PRODUCTS DIVISION -- HFD-560

NDA #: 20-281, SE2-016
SUBMISSION DATE: Feb. 23, 1999.
TYPE: Efficacy Supplement
REVIEW DATE: Dec. 20, 1999.
REVIEWER: John Hyde, Ph.D., M.D.

NAME: Ultram (tramadol HCl).
SPONSOR: R.W. Johnson
920 Route 202
P.O. Box 300
Raritan, NJ 08869
phone (908) 704-4600

PHARMACOLOGIC CATEGORY: Analgesic
PROPOSED INDICATIONS: Management of Pain
DOSAGE FORM & ROUTE: Scored tablets, oral, 50 mg

RELATED REVIEWS
Medical Officer Review of 7/1/99.
Chemistry Review of 9/7/99.

CSO: Y. Kong, Pharm.D.

RESUME:

Ultram was approved on 3/3/95 for management of pain with recommended dosing of 50 to 100 mg every 4 to 6 hours, not to exceed 400 mg/day. Supplement 014, approved on 8/21/98, included additional dosing information reflecting the results a study that showed dizziness and vertigo were reduced when Ultram was initiated with a titration regimen increasing the dose 50 mg/day every 3 days.

This supplement consists of two parts: the introduction of a scored tablet to allow a 25 mg dose, and labeling to reflect use of the 25 mg dose in a slower titration regimen (16-days) that was shown to reduce discontinuations for nausea and vomiting compared to more rapid titration.

The Chemistry Reviewer found the CMC changes acceptable and recommended approval. The Medical Reviewer agreed with the conclusions of the titration study and found the application approvable, pending some

modifications to the proposed labeling text, including removal of references to the previous 10-day titration study.

This reviewer agrees with the approvability of the application. However, some additional labeling changes are recommended, as discussed below.

DISCUSSION:

(See Medical Review for applicant's original proposed labeling text.)

The recommend dosing for ULTRAM is 50 to 100 mg every 4 to 6 hours not to exceed 400 mg/day. Without substantial evidence of efficacy data for the 25 mg dose, the recommended dosing should still be 50 to 100 mg. Evidence was not provided that the 25 mg dose will provide adequate acute pain relief, and is reasonable to presume it would not. The labeling should clearly reflect that the titration regimen is for chronic usage, where an immediate analgesic effect may not be required.

It is acceptable to include information about the previous titration study, since its results pertain to CNS, rather than GI effects. However reference to osteoarthritis (OA) patients should be eliminated, since OA is not an approved indication, and the fact of these patient having OA was incidental the major object of the trial was to study discontinuation due to the adverse events.

The section describing the clinical trial results is too wordy. **Suggested** wording is presented below.

Reference to titration study results can be removed from the DOSAGE AND ADMINISTRATION section, since the information is described in the clinical trials section.

Recommended changes to the labeling are presented on the next page:

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Discussions with the Applicant

The above recommended wording was faxed to the applicant 12/6/99. The applicant was contacted by telephone on 12/13/99. FDA staff was Yoon Kong, CSO, and Dr. Hyde. See separate telecon notes.

The applicant accepted FDA wording for the text describing the clinical trials, but wanted to include a graph comparing discontinuation for nausea and vomiting, showing results for the 10-day titration to 200 mg/day, the 13-day titration to 150 mg/day, and the 16-day titration to 200 mg/day. The applicant agreed to include the graph but to eliminate the 13-day titration to 150 mg/day, since 150 mg/day does not represent a recommended dosing regimen.

The applicant also proposed making changes the D&SAGE AND ADMINISTRATION section to describe the dose titration for chronic pain before, rather than after, the description of dosing for acute pain.

In subsequent fax communications, the applicant agreed to some editorial changes in the DOSAGE AND ADMINISTRATION section as reflected in draft text dated 12/14/99.

RECOMMENDATIONS:

The labeling proposed by the applicant in the submission dated 12/14/99 is acceptable and should be approved.

Since the applicant is currently investigating pediatric use of this product in response to a written request and is expecting to submit the data by March 2000, the requirement to submit pediatric data may be deferred to the earliest permitted date (12/2/00).

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Orig NDA #20-281
HFD-550/Div File
HFD-340
HFD-550/CSO/Kong
HFD-550/Chem/Ho
HFD-550/MO/JHyde

131
John E. Hyde, Ph.D., M.D.

12-20-99

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CENTER FOR DRUG EVALUATION AND RESEARCH

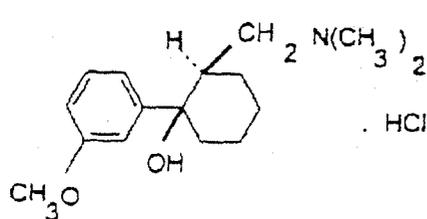
APPLICATION NUMBER: 020281/S016

CHEMISTRY REVIEW(S)

NDA 20-281

DIV

SEP - 7 1999

Chemistry Review #1	1. Division HFD-550	2. NDA Number 20-281
3. Name and Address of Applicant The R. W. Johnson Pharmaceutical Research Institute, 700 Route 202 SOL&, P. 0. Box 670 Raritan, NJ 08869-0602		4. Supplement Number Date 20-281/S-16 2/23/99
5. Name of Drug ULTRAM® Tablet		6. Nonproprietary Name Tramadol HCl tablets
7. Supplement Provides for: the addition of a score to the UL TRAM® 50 mg Tablet in order to allow physicians to prescribe a new titration dosing regimen at 25 mg.		8. Amendment(s) 3-8-99 8-25-99
9. Pharmacological Category	10. How Dispensed: Rx	11. Related Documents- None
12. Dosage Form Tablets	13. Potency(ies): 50 and 100 mg	
14. Chemical Name and Structure:  <p>TRAMADOL . HCl M. W. = 299.84 Formular: C₁₆ H₂₅ NO₂ .HCl</p> <p>APPEARS THIS WAY ON ORIGINAL</p>		
15. Comments: <div style="border: 1px solid black; height: 100px; width: 100%;"></div> <p>The results of these studies demonstrate that the UL TRAM® 50 mg scored tablets are equivalent to the current UL TRAM® 50mg tablets with</p>		
16. Conclusions and Recommendations: Recommend approval from the chemistry point of view.		

17. Name:	Review Chemist	Signature	Date
Bart Ho. Chemist	/S/	September 3, 1999	
Team Leader Hasmukh Patel	/S/ [Signature]	9/7/99 Date	

CC: NDA 20-281
 HFD-550/Division File
 HFD-550/Lewin
 HFD-550/B. Ho
 HFD-550/Patel
 HFD-930X. W. Chen

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Doc ID: 20281 S16SCOREABH

APPEARS THIS WAY
 ON ORIGINAL

CENTER FOIDRU(EVALUATION)ANIRESEARCH

APPLICATION NUMBER: 020281/S016

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS

Tramadol HCl Tablets 50 mg Scored

NDA 20-281/Supplement

ITEM 13: PATENT INFORMATION

Information required in accordance with 21 CFR § 314.53.

ULTRAM® (tramadol hydrochloride) tablets are not protected by patent.

US Patent No.	Expiration Date
3,652,589	March 26, 1989
3,830,934	August 20, 1991

Additional Exclusivity Information:

Waxman Hatch

Expiration Date: 2000, based on approval of NDA 20-281, March 3, 1995.

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EXCLUSIVITY SUMMARY FOR NDA # 20-281

SUPPL # SE2-016

Trade Name Ultram Tablets, 50 mg and 100 mg Generic Name Tramadol Hydrochloride Tablets

Applicant Name The R. W. Johnson Research Institute

HFD # 550

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION -NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

Y E S / / NO / /

b) Is it an effectiveness supplement?

YES / / NO / /

If yes, what type? (SE1, SE2, etc.)

SE2

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES / / NO / /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was nor simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change of claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES / X / NO / /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES / / NO / X /

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES / / NO / X /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / X / NO / /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-281 Ultram (tramadol)

NDA# _____

NDA# _____

I

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #I), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / / NO / /

if "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA x(s) -

NDA# _____

NDA# _____

NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant" This section should be completed only if the answer to PART. II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / NO /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from same other source, including the published literature) necessary to support approval of the application or supplement?

YES / NO /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES / NO /

APPEARS THIS WAY
ON ORIGINAL

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES / / NO / /

If yes, explain: _____

APPEARS THIS WAY
ON ORIGINAL

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES / / NO / X /

If yes, explain: _____

APPEARS THIS WAY
ON ORIGINAL

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

 CAPES - 47

APPEARS THIS WAY
ON ORIGINAL

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

APPEARS THIS WAY
ON ORIGINAL

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES / / ! NO / / Explain: _____

Investigation #2

IND # YES / / ! NO / / Explain: _____

APPEARS THIS WAY
ON ORIGINAL

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES / / Explain _____ ! NO / / Explain _____

APPEARS THIS WAY
ON ORIGINAL

Investigation #2

YES / / Explain _____ ! NO / / Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES / /

NO / /

If yes, explain: _____

/S/
Signature
Date 12/20/99
Title: Director

APPEARS THIS WAY
ON ORIGINAL

/S/
Signature of Office/
Date 12/21/99
Division Director

cc: Original NDA Division File HFD-93 Mary Ann Holovac

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE
(Complete for all original application and all efficacy supplements)

NDA/BLA Number: <u>20281</u>	Trade Name: <u>ULTRAM (TRAMADOL HCL) TABLETS</u>
Supplement Number: <u>16</u>	Generic Name: <u>TRAMADOL HYDROCHLORIDE</u>
Supplement Type: <u>SE2</u>	Dosage Form:
Regulatory Action: <u>AP</u>	Proposed Indication: <u>Management of moderate to moderately severe pain</u>

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

NeoNates (0-30 Days) Children (25 Months-12 years) Adolescents (13-16 years)
 Infants (1-24 Months) Adolescents (13-16 Years)

Label Adequacy Inadequate for ALL pediatric age groups
 Formulation Status
 Studies Needed
 Study Status

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

Sponsor has a written request letter for the original NDA 20-281.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, YOON KONG

Signature /S/

Date 12 20 99

BEST POSSIBLE COPY

APPEAR THIS WAY
UN
ORIGINAL

ITEM 16: DEBARMENT CERTIFICATION

The R.W. Johnson Pharmaceutical Research Institute certifies that we did not and will not use in any capacity the services of any person **debarred** under *subsections 306(a) or 306(b)* of the Federal Food and Drug and Cosmetic Act in connection with this New Drug Application.



Sandra c. Cottrell, PhD

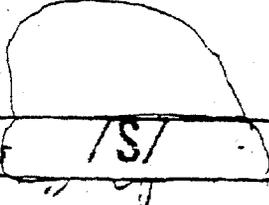
Director, Regulatory Affairs

The R.W. Johnson Pharmaceutical Research Institute

Route 202 P.O. Box 300

Raritan, New Jersey 08869-0602

APPEARS THIS WAY
ON ORIGINAL

RECORD OF TELEPHONE CONVERSATION/MEETING	DATE 8/17/99	
<p>Questions raised:</p> <p>We request that the firm commit to include the revised batch record in the next annual report. Firm is recommended to send the commitment to the reviewer by fax followed by an official amendment to this supplement (S-01 6).</p> <p>Response:</p> <p>Agreed.</p> <p style="text-align: center;">APPEARS THIS WAY ON ORIGINAL</p>	NDA NUMBER 20-281/S-016	
	IND NUMBER	
	TELECON/MEETING	
	INITIATED BY <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> APPLICANT/ <input type="checkbox"/> SPONSOR <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> FDA <input type="checkbox"/> <input type="checkbox"/>	MADE <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> BY TELEPHONE <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> IN PERSON <input type="checkbox"/> <input type="checkbox"/>
	PRODUCT NAME Tramadol HCl Tablet	
	FIRM NAME R.W. Johnson	
NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD Dr. Sandra Cottrell Director, Regulatory Affairs TELEPHONE 908-704-4600		
SIGNATURE 	DIVISION HFD-550	



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

FEB 23 1999



QUAD
SE2-016

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

NDA 20-281
ULTRAM® (tramadol
hydrochloride tablets)

NDA SUPPLEMENT
Scored 50mg ULTRAM® (tramadol
HCl tablets)
Dose Titration Labeling Change

Dear Sir/Madam:

Reference is made to NDA 20-281 for ULTRAM® (tramadol HCl tablets) approved on March 3, 1995, and its supplement S-014, approved August 21, 1998; to correspondence filed with the Agency to IND on May 1, 1997 and July 11, 1997 for Protocol CAPSS-047; and to correspondence filed to NDA 20-281 on October 13, 1997 with regard to a 50 mg scored tablet.

At this time, the R. W. Johnson Pharmaceutical Research institute is submitting a supplement to NDA 20-281 containing Chemistry, Manufacturing and Controls information supporting the scoring of the 50 mg tramadol hydrochloride tablet, the final study report for Protocol CAPSS-047, and proposed labeling changes to further enhance compliance and tolerability of the product.

- The Chemistry, Manufacturing and Controls information contains data to support the physical/chemical qualification of a 50 mg scored tablet. We have provided finished product specifications for the 50 mg scored tablet.
- Final study results of Protocol CAPSS-047 indicate that the slower titration regimen of tramadol hydrochloride (25 mg increments every 3-days) significantly reduced the incidence of discontinuation due to adverse events, especially nausea and/or vomiting.
- This supplement contains proposed labeling changes to the Clinical Studies, DOSAGE and ADMINISTRATION and SUPPLIED sections of our current package insert. New text is provided under the Clinical Studies section which incorporates descriptions of the double-blind Study Protocol CAPSS-047: "An Evaluation of the Effect of Titration Schedules of ULTRAM® (tramadol HCl) in

Subjects with Chronic Pain", provided herein. The Clinical Studies section also describes the double-blind study showing the benefits of slowed titration (Study Protocol TPS-D0S, "An Evaluation of Varying Titration Rates of ULTRAM® Tramadol HCl (RWJ 26898-002) in Subjects with Chronic Pain of Osteoarthritis" [redacted] as provided in support of NDA 20-281/S-014, approved August 21, 1998).

For ease of review, we are providing a side-by-side text comparison of the current version (Package Insert 635-19-227-4) and the new version of the final product labeling incorporating the proposed changes. We will provide the Agency with the new numerical identifier for the final product labeling associated with this supplement after approval and upon submission of the final product labeling to the FDA. A diskette containing the running text for this new version of the final product labeling in Microsoft Word 7.0 format, as well as hard copy of this document, are appended.

User Fee check payment in the amount of [redacted] was submitted January 13, 1999 under User Fee ID No. [redacted]. A copy of the Form FDA 3397 is provided herein.

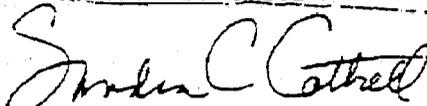
In addition at this time in accordance with 21 CFR § 314.50(j), we state that this supplemental application, upon approval by the U.S. Food and Drug Administration, is entitled to a three year period of marketing exclusivity under provisions of 21 CFR § 314.108(b)(5), and respectfully request the granting of this exclusivity. We certify that the study upon which this supplemental application relies is a "new clinical investigation" that is "essential to approval of the proposed labeling changes in this supplement, and was "conducted or sponsored by the applicant" within the meaning of 21 CFR § 314.108(a).

The archival and review copies of this supplement are enclosed. As required by CFR § 314.71(b), we certify that a field copy containing a true copy of the *Chemistry, Manufacturing and Controls* section, 21 CFR § 314.50(d)(1), and a copy of the application form required under 21 CFR § 314.50(a) (Form FDA 356h) has been provided directly to the FDA District Office in North Brunswick, New Jersey.

Should you have any questions please contact me directly at (908) 704-4033 or our phone number dedicated for FDA use at (908) 704-4600.

Sincerely,

The R.W. Johnson
Pharmaceutical Research Institute



Sandra Cottrell, Ph.D.
Director
Regulatory Affairs

cc: Lt. Cmdr. D'Annie Gunter (HFD-550) (Letter only)



THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0300

MAR - 8 1999

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

NDA 20-281

ULTRAM* (tramadol
hydrochloride tablets)

CORRESPONDENCE

Transmission of missing volumes
NDA Supplement S-016

Dear Sir/Madam:

Reference is made to NDA 20-281 for ULTRAM* (tramadol HCl tablets) approved on March 3, 1995, its supplement S-016, submitted February 23, 1999, and a telephone call placed by Lt. Cmdr. D'Annie Gunter, Project Manager for the product. Lt. Cmdr. Gunter identified that the archival copy of this supplement was missing four volumes in transmittal. We have clarified that these are Volumes 9 through 12 and are providing them at this time.

Please accept our apology for this omission.

Should you have any questions please contact me directly at (908) 7044033 or our phone number dedicated for FDA use at (908) 704-4600.

Sincerely,

The R.W. Johnson
Pharmaceutical Research Institute

Sandra Cottrill, Ph.D.
Director
Regulatory Affairs

cc: Lt. Cmdr. D'Annie Gunter (HFD-550) (Letter only)

Should you have any questions please contact me directly at (908) 704-4033 or our phone number dedicated for FDA use at (908) 704-4600.

Sincerely,

The R. W. Johnson
Pharmaceutical Research Institute

Sandra C. Cottrell

Sandra Cottrell, Ph.D.
Director
Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

cc: Mr. Anthony Zecolla (HFD-550) (Letter only)

APPEAR THIS WAY
ON ORIGINAL



ORIGINAL

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 202, P.O. BOX 200, RARITAN, NEW JERSEY 08869-0202

APR 16 1999

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

NDA 20-281
ULTRAM® (tramadol
hydrochloride tablets)

Correspondence
S-016 Scored 50mg ULTRAM® (tramadol
HCl tablets) - Response to FDA
Request for Electronic Copy of Clinical
Reports

Dear Sir/Madam:

SE2-016
EM

Reference is made to NDA 20-281 for ULTRAM® (tramadol HCl tablets) approved on March 3, 1995, and to Supplement S-016 filed on February 23, 1999 to provide for a Chemistry, Manufacturing and Controls amendment supporting the scoring of the 50 mg tramadol hydrochloride tablet, and proposed labeling changes to provide for titration of the product, to further enhance compliance and tolerability of the product. Reference is also made to a voice mail message received by Dr. Sandra Cottrell (R. W. Johnson Pharmaceutical Research Institute) on April 14, 1999 from Dr. Constance Lewin (HFD-550), requesting a CD-ROM containing electronic copies on CD-ROM of the two clinical studies provided in that submission.

In response to this request, enclosed is a CD-ROM containing electronic copies of clinical study reports for CAPSS-047: "An Evaluation of the Effect of Titration Schedules of ULTRAM® (tramadol HCl) in Subjects with Chronic Pain" and TPS-D0S, "An Evaluation of Varying Titration Rates of ULTRAM® Tramadol HCl (RWJ 26898-002) in Subjects with Chronic Pain of Osteoarthritis". Please note that these documents are provided in Microsoft WORD 7.0, for OFFICE 95.

Should you have any further questions or requests, please contact me directly at (908) 7044033 or our phone number dedicated for FDA use at (908) 704-4600.

Sincerely,

Sandra Cottrell, Ph.D
Director
Regulatory Affairs



DUPLICATE
NC
(S-016)

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE

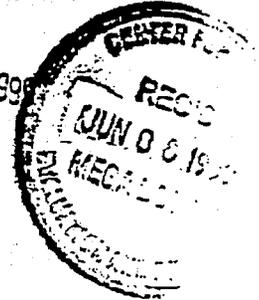
ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08849-0302

SUPPL NEWCORRESP JUN - 7 1999

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products (HFD-550)
Attn: Document Control Room N115
9201 Corporate Boulevard
Rockville, Maryland 208 50

NDA 20-281
ULTRAM® (tramadol
hydrochloride tablets)

CORRESPONDENCE
Response to Agency
Request for Electronic Copies
of Current Labeling and Proposed
Dose Titration Labeling Change



Dear Sir/Madam:

Reference is made to NDA 20-281 for ULTRAM® (tramadol HCl tablets) approved on March 3, 1995, and to a Supplement (S-016) submitted on February 23, 1999, to provide for a 50 mg scored tablet and a titration labeling change.

In response to a voice mail request from Dr. Constance Lewin, Project Manager, we are hereby providing a diskette (WORD 6.0, Windows 95) with the current labeling for ULTRAM® (tramadol HCl tablets) and the labeling proposed in our February 23, 1999 submission (S-016). Dr. Lewin noted that the electronic copies of the labeling were requested by the Medical Reviewer for ULTRAM.

If I can be of further assistance, please contact me at (908) 704-4033 or use our number dedicated to FDA USC, (908) 704-4600.

Sincerely,

Sandra C. Cottrell

Director
Regulatory Affairs

Natasha Rogozenski

Assistant Director
Regulatory Affairs



THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 212, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0302

DEC 22 1999

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products (HFD-550)
Attn: Document Control Room NI 15
9201 Corporate Boulevard
Rockville, Maryland 20850

NDA 20-281

ULTRAM[®] (tramadol
hydrochloride tablets)

CORRESPONDENCE

Final Labeling for 50-mg Scored Tablet
and
Dose Titration Labeling Change (S-016)

Dear Sir/Madam:

Reference is made to NDA 20-281 for ULTRAM[®] (tramadol HCl tablets) approved on 03 March 1995, and to a Supplement (S-016) submitted on 23 February 1999, to provide for a 50 mg scored tablet and a titration labeling change. Reference is also made to correspondences to this supplement by The R.W. Johnson Pharmaceutical Research Institute (RWJPRI) on 07 June 1999, 02 December 1999 and 14 December 1999.

On 14 December 1999, RWJPRI provided the final, running text version of the revised draft labeling to support our 23 February 1999 submission (S-016) along with an electronic copy of this final proposed new labeling (WORD 7.0, Windows 95/Office 97) which reflected the full exchange of dialogue and FAXed text between the Agency and RWJPRI. In a teleconference with Dr. Yoon Kong on 21 December 1999, we notified the Agency of an error in Figure 2 of the package insert which depicts the time to discontinuation due to nausea/vomiting. A problem with a old version of the software caused a minor error in the data plot. The correct version of Figure 2 is included in this submission along with the editorial changes FAXed from the Agency on 21 December 1999. RWJPRI agrees with the FDA reviewer's recommended changes to our submission of final proposed new labeling dated 14 December 1999 with one clarification which follows:

DOSAGE AND ADMINISTRATION

At this time, we are providing the corrected final running text and the corresponding electronic copy.

APPEARSTHISWAY
ON ORIGINAL

NAULTRAMscored50mgSNDAPackage InsertFinal run text and Dose Titration Labeling.1222 99.doc

If I can be of further assistance, please contact me at (908) 704-4222 or USC our number dedicated to FDA use, (908) 704-4600.

Sincerely,

The RW. Johnson
Pharmaceutical Research Institute

Natasha Rogozenski

Natasha Rogozenski

Assistant Director
Regulatory Affairs

cc: Yoon Kong PharmD (HFD-550) additional copy, including diskette, via Courier

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

LAST PAGE

ORIGINAL



THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08969-0302

NDA SUPPL AMEND

SEZ 016
OC

ATTACHMENT 1

APPENDIX 1

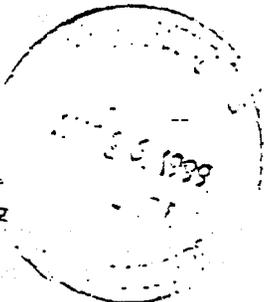
AUG 25 1999

Dr. Constance Lewin (HFD-550)
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V
Division of Anti-inflammatory, Analgesic
and Ophthalmic Drug Products (HFD-550)
9201 Corporate Boulevard
Rockville, Maryland 20850

NDA 20-281
ULTRAM®
(tramadol HCl tablets)

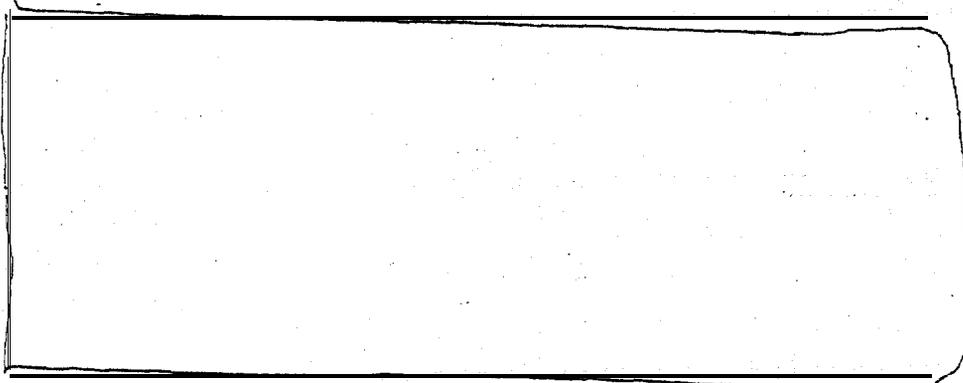
NDA Supplement S-016

Amendment
Response to Reviewing
Chemist Request



Dear Dr. Ho:

Pursuant to our telephone discussion of 17 August 1999, this letter, being provided both as a FAX and subsequent correspondence to the NDA file, serves to make the following commitment regarding NDA 20-281 supplement S-015, (Scored 50 mg ULTRAM® (tramadol HCl tablets) submitted 23 February 1999:



Noted
S/L
9-2-99

SEI-018/RL
8.20
8.23

If you have any questions concerning this submission, please contact me at (908) 704-4033, or use our phone line dedicated for FDA use, (908) 704-4600.

Sincerely,

Sandra C. Cottrell

Sandra C. Cottrell, PhD
Director
Regulatory Affairs

Natasha Rogozenski

Natasha Rogozenski
Assistant Director
Regulatory Affairs

cc: Dr. Constance Lewin (W-550)
Dr. Bartholome Ho (HFD-550)

APPEARS THIS WAY
ON ORIGINAL

ATTACHMENT 1

APPENDIX 1

551-018/BL

8.20.9
8.23.9

ORIGINAL



THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 202, P.O. BOX 300, PARITAN, NEW JERSEY 08859-0302

NDA SUPPL AMEND

582-016

OC

ATTACHMENT 1

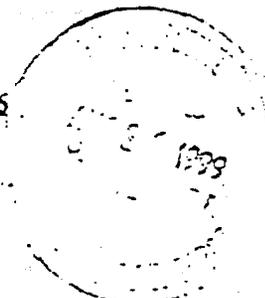
AUG 25 1999

Dr. Constance Lewin (HFD-550)
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V
Division of Anti-inflammatory, Analgesic
and Ophthalmic Drug Products (HFD-550)
920 I Corporate Boulevard
Rockville, Maryland 20850

NDA 20-281
ULTRAM®
(tramadol HCl tablets)

NDA Supplement S-016

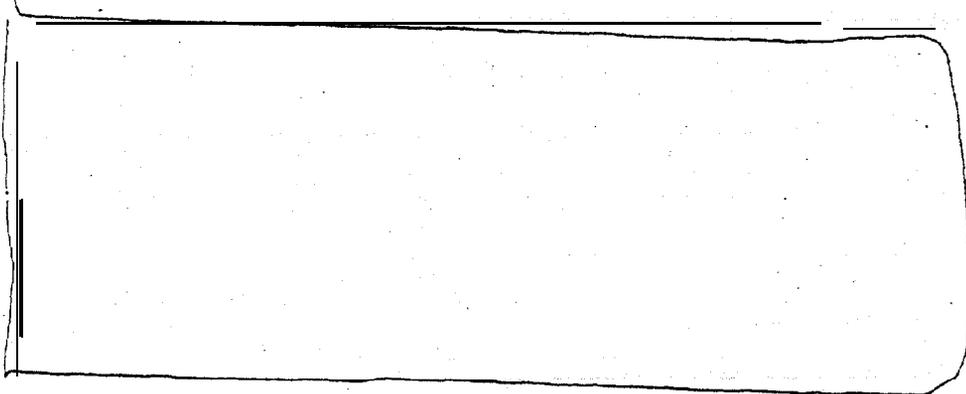
Amendment
Response to Reviewing
Chemist Request



APPENDIX 1

Dear Dr. Ho:

Pursuant to our telephone discussion of 17 August 1999, this letter, being provided both as a FAX and subsequent correspondence to the NDA file, serves to make the following commitment regarding NDA 20-281 supplement S-015, (Scored 50 mg ULTRAM® (tramadol HCl tablets) submitted 23 February 1999:



Noted
9-2-99

581-018/62

B.20
B.22

ORIGINAL 

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0302

NDA SUPPL AMEND

SEZ-016
BL

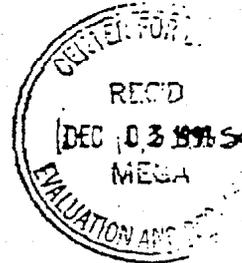
December 2, 1999

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

NDA 20-281
ULTRAM[®] (tramadol
hydrochloride tablets)

CORRESPONDENCE

Response to Agency
Request for Electronic Copy of Proposed
Dose Titration Labeling Change (S-O 16)



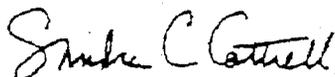
Dear Sir/Madam:

Reference is made to NDA 20-281 for ULTRAM[®] (tramadol HCl tablets) approved on March 3, 1995, and to a Supplement (S-016) submitted on February 23, 1999, to provide for 50 mg scored tablet and a titration labeling change, as well as to a correspondence to that Supplement in which the The RW. Johnson Pharmaceutical Research Institute (RWJPRI) responded to a voice message request from Dr. Constance Lewin, Project Manager, to receive an additional copy of the diskette (WC&D 6.0, Windows 95) with the current labeling for ULTRAM[®] (tramadol HCl tablets) and the labeling proposed in our February 23, 1999 submission (S-016).

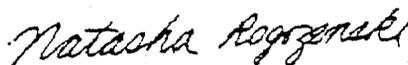
At this time, in response to a telephone request on December 2, 1999 by Ms. Yoong Kong, the new Project Manager, RWJPRI is providing an additional electronic copy of the proposed new labeling (WORD 6.0, Windows 95) associated with our February 23, 1999 submission (S-016).

If I can be of further assistance, please contact me at (908) 704-4033 or use our number dedicated to FDA use, (908) 704-4600.

Sincerely,



Sandra C. Cottrell
Director
Regulatory Affairs



Natasha Rogozenski
Assistant Director
Regulatory Affairs

Desk copy: Ms. Yoong Kong, Project Manager (HFD-550)

1621
J. H. [unclear] 12-10-99



THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE

DEC 14 1999

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

NDA 20-281
ULTRAM[®] (tramadol
hydrochloride tablets)

CORRESPONDENCE

Final Proposed Labeling
and Diskette for 50-mg Scored Tablet
and Dose Titration Labeling Change (S-016)

Dear Sir/Madam:

Reference is made to NDA 20-281 for ULTRAM[®] (tramadol HCl tablets) approved on March 3, 1995, and to a Supplement (S-016) submitted on February 23, 1999, to provide for a 50 mg scored tablet and a titration labeling change. In response to Agency requests, additional diskette copies of the draft labeling were provided as correspondences to this supplement by the The R.W. Johnson Pharmaceutical Research Institute (RWJPRI) on June 7, 1999 and December 2, 1999.

Reference is also made to a FAXed communication by the Agency on December 6, 1999 with alternative labeling text under the sections Clinical Studies and DOSAGE AND ADMINISTRATION. RWJPRI FAXed a slight modification text proposal on December 10, 1999, in anticipation of a teleconference between the Agency and RWJPRI on December 13, 1999. Subsequent to that meeting and discussions therein, on December 14, 1999 the Agency provided another FAX of text reflecting the discussions of changes agreed upon, as well as minor additional edits.

At this time, RWJPRI is providing the final, running text version of the revised draft labeling to support our February 23, 1999 submission (S-O 16) along with an electronic copy of this final proposed new labeling (WORD 7.0, Windows 95/Office 97). This text reflects all exchange of dialogue and FAXed text between the Agency and RWJPRI.

If I can be of further assistance, please contact me at (908) 704-4033 or use our number dedicated to FDA use, (908) 704-4600.

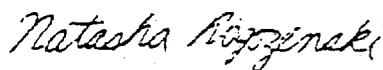
Sincerely,

Sandra C. Cottrell



Director
Regulatory Affairs

Natasha Rogozenski



Assistant Director
Regulatory Affairs

cc: Yoon Kong (HFD-550) additional copy, including diskette, via Federal Express

APPEARS THIS WAY
ON ORIGINAL

Volume 1, Number 1, January 1984

U.S. GOVERNMENT PRINTING OFFICE: 1984 O-242-100

Federal Register Notices

Volume 1, Number 1, January 1984

U.S. GOVERNMENT PRINTING OFFICE: 1984 O-242-100

DEPARTMENT OF HEALTH AND
HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 2, 5, 10, 310, 314, 320,
and 413

[Docket No. 85N-0214]

RIN 0905-AB63

Abbreviated New Drug Application
Regulations

AGENCY: Food and Drug Administration,
HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing final regulations for most of its requirements for abbreviated new drug applications (ANDA's). FDA published a proposed rule for ANDA's in the Federal Register of July 10, 1989 (54 FR 28872). These regulations implement title I of the Drug Rice Competition and Patent Term Restoration Act of 1984 (Pub. L. 98-417) [the 1984 amendments]. This final rule covers subjects such as ANDA content and format, approval and nonapproval of an application and suitability petitions. This rule does not finalize the provisions of the proposed rule on patent certification and market exclusivity. FDA is still examining the issues pertaining to those provisions and will finalize them in a future edition of the Federal Register.

EFFECTIVE DATE: The regulations will become effective on June 29, 1992.

FOR FURTHER INFORMATION CONTACT:

Philip L. Chao, Center for Drug Evaluation and Research (HFD-362), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20867, 301-295-8048.

SUPPLEMENTARY INFORMATION:

I. Background

A. New Drug Approval: 1938 to 1962

In 1938, Congress passed the Federal Food, Drug, and Cosmetic Act (the act). The act created a premarket approval system for drug products that required applicants seeking drug product approval to submit a new drug application (NDA) to FDA. The NDA would contain information demonstrating, among other things, that the drug product was safe. The act also provided that an NDA would automatically become effective (i.e., the product could be lawfully marketed) within a fixed period unless the agency affirmatively refused to approve the application.

In addition to drug products that had an effective NDA, many products were

marketed without effective applications. These products were identical, similar, or related to products with effective NDA's. The manufacturers of these products had concluded that their drug products were generally recognized as safe, or had received advisory opinions from FDA that an NDA was not required because the products were generally recognized as safe.

In 1962, Congress amended the drug approval provisions of the act to require affirmative approval to NDA's before marketing. The amendments required applicants to show that their products were both safe and effective [Pub. L. 87-781 (October 10, 1962)]. Thus, on or after October 10, 1962, a person could not market a new drug without an approved NDA that contained sufficient safety information as well as substantial evidence establishing the drug's effectiveness for its intended uses.

The 1962 amendments also deem NDA's that had become effective before October 10, 1962, to be approved. As with postenactment drugs, the 1962 amendments required these "pre-1962" drugs to be shown to be effective for their intended uses. Consequently, FDA began a program to evaluate the drugs that had been deemed approved to determine whether there was substantial evidence of their effectiveness. This systematic evaluation and the implementation of FDA's findings became known as the Drug Efficacy Study Implementation (DESI). Under DESI, FDA contracted with the National Academy of Sciences/National Research Council (NAS/NRC), which established expert panels to review available evidence of effectiveness and to provide recommendations to FDA. FDA considered the NAS/NRC panels' recommendations about the effectiveness of these DESI drugs, and announced its conclusions through Federal Register notices. These notices, known as DESI notices, contain the acceptable marketing conditions for the class of drug products covered by the notice.

*Both ANDA Procedure for
Drugs* Pre-1962

If a manufacturer had a pre-1962 NDA in effect for a drug product, FDA continued its approval if the manufacturer submitted a supplemental new drug application to conform to the product's indications for use to those determined to be effective in the DESI review. Yet, as stated above, many drug products had active ingredients and indications that were identical or very similar to the drug products found to be effective in the DESI review but lacked

NDA's themselves. In implementing the DESI program with respect to these duplicate products, FDA concluded that each such drug product was a "new drug" that required its own approved NDA before it could be legally marketed (*United States v. Generix Drug Corp.*, 460 US. 453 (1983)). Additionally, FDA issued a policy statement in the Federal Register of May 28, 1988 (33 FR 7756) that revoked the earlier advisory opinions that drugs could be marketed without prior FDA clearance. This rule was codified at 21 CFR 310.100.

Shortly thereafter, FDA created the ANDA procedure for the approval of duplicate products in reliance on the DESI evaluation. In brief, after the DESI program had found a particular drug product to be effective and suitable for ANDA's, FDA published a Federal Register notice announcing its conclusions. Any manufacturer of a duplicate drug product that did not have an approved NDA was then required to submit an ANDA to obtain approval to market the duplicate version of the approved drug. (See 34 FR 2673, February 27, 1969; 35 FR 6574, April 24, 1970; and 35 FR 11273, July 14, 1970.)

Before 1964, FDA based these ANDA approval on the theory that the evidence of effectiveness necessary for approval of an NDA had been provided, reviewed, and accepted during the DESI process. Evidence of the drug's safety had been determined on the basis of information contained in the pioneer NDA and by the subsequent marketing experience with the drug. FDA required ANDA applicants to submit information that showed the applicant's ability to manufacture a product of acceptable quality whose safety and effectiveness were equivalent to the drug product whose safety and effectiveness had been established. Thus, ANDA applicants provided information on the drug product's formulation, manufacture, quality control procedures, and labeling. DESI notices specified additional information, such as bioavailability/bioequivalence data, for the ANDA.

C. Procedures for Duplicates of Post-1962 Drugs ("Paper NDA" Policy)

FDA never extended its ANDA policy far pre-1962 drugs to duplicates of drugs first approved for marketing on or after October 10, 1962, although it did consider the possibility of such an extension either by regulation or through legislation. (See 54 FR 28872 at 28873 and citations therein.) As patents began to expire for many post-1962 drugs, including some high volume, therapeutically important drug products.

Section 314.120—Not Approvable Letter to the Applicant

Proposed § 314.120 described the circumstances under which FDA would send a not approvable letter. Proposed § 314.120(a)(1) and (a)(2) would require applicants to amend, withdraw, or notify FDA of an intent to amend an application or abbreviated application. Proposed § 314.120(a)(3) would permit applicants to ask FDA to provide a hearing on the question of whether there are grounds for denying approval of the application under section 505(d) or (j)(3) of the act. Applicants would be required to respond to a not approvable letter within 10 days, except that ANDA applicants, under proposed § 314.120(b), would have 180 days to respond.

65. Most comments on proposed § 314.120 recommended changes to response times. One comment suggested amending § 314.120(a) to give applicants 30 days to respond to a not approvable letter. Two comments asked that the regulation require ANDA applicants to respond to a not approvable letter within 10 days rather than the 180 days given at § 314.120(b).

FDA declines to amend the rule as suggested by the comments. The comments did not contain any justification for revising the response times, and FDA sees no reason to do so.

69. One comment asked that proposed § 314.120(a)(3) be revised to make clear that ANDA and NDA applicants, upon receipt of a not approvable letter, have the right to request that the agency provide the applicant an opportunity for a hearing.

Section 314.120(a)(3) was intended to apply to both ANDA applicants and to NDA applicants. FDA, therefore, agrees with the comment and has revised the provision accordingly. FDA has also revised § 314.120(b) to clarify that an ANDA applicant must make its request for a hearing to FDA within 10 days after the date of the not approvable letter.

Section 314.122—Submitting on Abbreviated Application for, or a 505(j)(2)(C) Petition That Relies on, a Listed Drug That is no Longer Marketed

70. One comment suggested that the title be revised to read, "Submitting an Abbreviated Application for . . ." The comment said this change would be consistent with the definitions in § 314.3

FDA agrees and has revised the title accordingly.

Section 314.125—Refusal to Approve an Application or an Abbreviated Antibiotic Application

FDA received no comments on this provision and has finalized it without substantive change.

Section 314.127—Refusal to Approve an Abbreviated New Drug Application

Proposed § 314.127 provided a list of reasons for refusing to approve an ANDA. In general, these reasons corresponded to those listed at section 505(j)(3) of the act.

71. One comment asked FDA to amend proposed, § 314.127(c) to describe the type of information that it would require an ANDA applicant to submit to show that an active ingredient in an ANDA product is the same as the active ingredient in the reference listed drug. In brief, proposed § 314.127(c) would, in relevant part, have FDA refuse to approve an ANDA if there is insufficient information to show that the active ingredient(s) in the proposed drug product are the "same" as those in the reference listed drug.

Under 21 CFR 314.120, if FDA believes that an application is not approvable, it will notify the applicant in writing and describe the deficiencies in the application. Thus, in the situation described by the comment, the applicant could use the agency's written response to determine how it could demonstrate that its active ingredient is the same as that in the reference listed drug.

Depending upon the circumstances, an applicant might find additional guidance in drug compendia or FDA guidelines. (See paragraph 28 above for a related comment.) The comment's suggestion, therefore, is unnecessary.

72. Proposed § 314.127(g) (now § 314.127(a)(7)) would permit FDA to refuse to approve an abbreviated application if information in the ANDA "is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for the listed drug . . . except for changes required because of differences approved in a petition under § 314.93 or because the drug product and the reference listed drug are produced or distributed by different manufacturers." One comment said FDA should also require ANDA holders to obtain current labeling for the listed drug every 6 months and update their own labeling accordingly.

FDA has revised § 314.150 to require ANDA holders to maintain current labeling. Failure to do so may result in withdrawal of approval. FDA will not, however, require ANDA holders to obtain current labeling or to update their own labeling every 6 months because

drug labeling does not change on a regularly scheduled basis.

73. A second comment recommended adding "or because of patent requirements" to the end of proposed § 314.127(g).

FDA agrees that a patent may be a valid reason for labeling differences between the reference listed drug and the ANDA drug product and that such differences should not be a basis for refusing to approve an ANDA. FDA has, therefore, revised the rule to indicate that labeling differences may also be due to patents or exclusivity. However, FDA cautions that it will not approve an ANDA with different labeling if the labeling differences affect product safety or efficacy. For example, if the patent protects information on a new dosing regimen and FDA concludes that the preexisting dosing regimen is unsafe, the different labeling for the proposed ANDA product would be grounds for refusing to approve the ANDA.

74. Proposed § 314.127(h)(1)(i) (now § 314.127(a)(8)(i)(A)) would permit FDA to refuse to approve an ANDA if FDA had any information that the proposed drug product's inactive ingredients are unsafe for use under the conditions prescribed, recommended, or suggested in the proposed drug product's labeling. Proposed § 314.127(h)(1)(ii) [now § 314.127(a)(8)(i)(B)] would permit FDA to refuse to approve an ANDA if the proposed drug product's composition was unsafe under the conditions prescribed, recommended, or suggested in the proposed labeling because of the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included. One comment asked FDA to merge proposed § 314.127(h)(1)(i) and (h)(1)(ii) or to explain their differences.

FDA declines to revise the rule as suggested. Section 314.127(a)(8)(i)(A) and (a)(8)(i)(B) (proposed § 314.127(h)(1)(i) and (h)(1)(ii)) reflects the statutory language at section 505(j)(3)(H)(i) and (j)(3)(H)(ii) of the act, respectively, and serves different purposes. To illustrate, if FDA concluded that an inactive ingredient in a proposed ANDA product was unsafe, it could refuse to approve the ANDA under § 314.127(a)(8)(i)(A). If the proposed ANDA product involved a combination of inactive ingredients and the combination (as opposed to each inactive ingredient), either by the type or quantity of an inactive ingredient or the manner of formulation of the inactive ingredients into the product, shows that the product was unsafe, the refusal to approve the ANDA would occur under § 314.127(a)(8)(i)(B).

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1900 ARLINGATE LANE
COLUMBUS
(614)276-4000

ACC# 204803439
ACTUAL WGT: 7 LBS SCALE

TO: DOCKETS MANAGEMENT BRANCH
FOOD AND DRUG ADMINISTRATION
5630 FISHERS LANE, ROOM 1061

ROCKVILLE MD 20852

4103 8816 9092



REF: KRYSY HOANE

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TRK# 4103 8816 9092 Form 0201

Deliver by:
02OCT01

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153077-127 FIT 05/00



DIAMOND LABORATORIES INC
1900 ARLINGATE LANE
COLUMBUS OH 43228-4112
(614) 276-4000

ACC# 204803439
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FOOD AND DRUG ADMINISTRATION
5630 FISHERS LANE, ROOM 1061

ROCKVILLE MD 20852

4103 8816 9092

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REF: KRISTY HOANE

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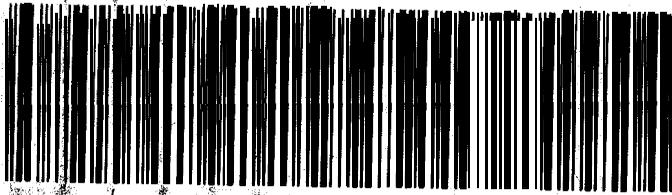
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