CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-123

ADMINISTRATIVE DOCUMENTS

ITEM 13: PATENT INFORMATION

Information required in accordance with 21 CFR § 314.53.

US Patent No.	Expiration Date
5,336,691	August 9, 2011 (eligible for patent term extension)

Re: NDA 21-123 (tramadol hydrochloride/acetaminophen tablets)
Information required in accordance with 21 CFR § 314.53

Pursuant to the provisions of 21 CFR § 314.53, attached hereto please find patent information for the above identified application.

The attached Item 13 lists 1 patent. The undersigned declares that U.S. Patent No. 5,336,691 covers the formulation and composition of the tramadol hydrochloride/acetaminophen combination . This product is the subject of this application for which approval is being sought.

Respectfully submitted,

Ralph R. Palo
Registered Patent Attorney
Reg #29,486

EXCLUSIVITY SUMMARY for NDA # 21-123
Trade Name: Ultracet
Generic Name: Tramadol hydrochloride/ acetaminophen
Applicant Name: R.W. Johnson Pharmaceutical Research Institute
HFD-550
Approval Date: 15-August-01

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 questions about the submission.

   a) Is it an original NDA? YES/_X__/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /X /

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

   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 /__X_/ 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 not 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 or 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?

5 years

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

YES /___/ NO /__X _/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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 9.

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 9 (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 the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

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 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 /__X_/ NO /___/

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

NDA # 20-281 Tramadol

NDA # 7-289 Acetaminophen Combo

NDA # 8-734 Acetaminophen

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. 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.

YES /_X__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(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 /_ X __/ 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 9:

_____

_____

(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 /_ X __/

If yes, explain: _____

_____

(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: _____

_____

(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:

Investigation #1, Study # TRAMAP-ANAG-010, 012, 013, [redacted]

Investigation #2, Study # PROTOCOLS TRAMAP-ANAG-002, 003

Investigation #3, Study # STUDY TRAMAP-ANAG-004 & 005

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 /___/ NO /__ X _/

Investigation #2 YES /___/ NO /_ X __/

Investigation #3 YES /___/ NO /__ X _/

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

was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(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 /__ X _/

Investigation #2 YES /___/ NO /__ X _/

Investigation #3 YES /___/ NO /__ X _/

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

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(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"):

Investigation #1, Study # TRAMAP-ANAG-010, 012, 013, [redacted]

Investigation #2, Study # PROTOCOLS TRAMAP-ANAG-002, 003

Investigation #3, Study # STUDY TRAMAP-ANAG-004 & 005

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.

APPEARS THIS WAY
ON ORIGINAL

(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 # [redacted] YES /_X__/	NO /___/ Explain: _____
	_____
	_____
Investigation #2	
IND # [redacted] YES /_ X __/	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 _____
_____	_____
_____	_____

(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 /_ X __/

If yes, explain: _____

_____

_____

Barbara J. Gould *17-August-01*
Signature of Preparer Date
Title: Project Manager

_____ _____
Signature of Office or Division Director Date

cc:
Archival NDA
HFD-550/Division File
HFD-550/Walling/Gould/RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	21123	**Trade Name:**	ACETAMINOPHEN 325MG/TRAMADOL HCL 37.5MG
Supplement Number:		**Generic Name:**	ACETAMINOPHEN /TRAMADOL HCL
Supplement Type:		**Dosage Form:**	Tablet; Oral
Regulatory Action:	NA	**Proposed Indication:**	Management of [redacted] acute [redacted] pain.

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)
____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Does Not Apply
Formulation Status	NEW FORMULATION developed with this submission
Studies Needed	
Study Status	

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

COMMENTS:
Sponsor submitted Pediatric Deferral on September 14, 1999.

Sponsor requested Pediatric Deferral on September 14, 1999 pending assessment of the data from the ongoing clincial program for Ultram (NDA 20-28[redacted] Sponsor has not yet submitted a proposal for usage of this combination drug product (tram/apap) in the pediatric population.

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

/S/ 6-8-00

Signature Date

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

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

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANTI-INFLAMMATORY, ANALGESIC, AND OPHTHALMIC DRUG PRODUCTS
HFD-550, 9201 Corporate Blvd, Rockville MD 20850 Tel:(301)827-2040

Application Information

NDA #: 21-123
Sponsor: The R.W. Johnson Pharmaceutical Research Institute.

Original Receipt Date: August 31, 1999
Completion Date: June 16, 2000

Financial Disclosure Assessment

The sponsor has provided financial information for investigators/subinvestigators involved in all studies for NDA 21-123.

There is no any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigators could be affected by the outcome of the three pivotal dental pain studies, the supporting single dose studies [redacted]

[redacted]

In short, the financial disclosure information is adequate, and there is no serious concern on the integrity of the data submitted under this NDA.

/S/ 6/16/2000

Chang Lee, MD, Ph.D.
Medical Officer

cc NDA 21-123
HFD-520/DN Files
HFD-550/Kong/M.Lthman

NOV 12 1999

CONSULTATION REQUEST/RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE SENT: November 10, 1999	**DUE DATE: N/A**	**OPDRA CONSULT #:** 99-067

TO (Division): Karen Midthun, M.D.
Acting Director, Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products
(HFD-550)

PRODUCT NAME: Ultracet™ (Tramadol/ Acetaminophen) **NDA#:** 21-123	**MANUFACTURER:** R.W. Johnson Pharmaceutical Research Institute

CASE REPORT NUMBER(S): N/A

SUMMARY:

In response to the request by the Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products, OPDRA conducted a review of the potential name confusion of the proposed proprietary name, Ultracet™ with other approved proprietary/generic names. This review includes studies conducted within OPDRA with emphasis on the evaluation of the potential medication errors in handwriting and verbal communication of the proposed proprietary name.

OPDRA RECOMMENDATION:

OPDRA has no objections to the use of the proprietary name, Ultracet™. See review.

/S/ 11/12/99
Jerry Phillips
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3246
Fax: (301) 827-5189

/S/ 11/12/99
Peter Honig, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm 15B-03
Center for Drug Evaluation and Research

Proprietary Name Review

DATE OF REVIEW: November 10, 1999

NDA#: 21-123

NAME OF DRUG: Ultracet™
(tramadol hydrochloride / acetaminophen tablets)
37.5 mg / 325 mg

NDA HOLDER: R.W. Johnson Pharmaceutical Research Institute

I. INTRODUCTION

This consult is in response to a request sent on October 21, 1999, from the Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products to review a proposed proprietary drug name, Ultracet, regarding potential name confusion with other proprietary/generic drug names. The container labels and carton labeling were not available for review of possible interventions in minimizing medication errors.

The proposed proprietary name, Ultracet, was previously reviewed by the Labeling and Nomenclature Committee (LNC) and was found to be unacceptable. The LNC indicated that Ultracet was unacceptable due to the fact that it sounds like an "ultra acetaminophen" and thereby implies that the more important ingredient is acetaminophen.

In a letter dated September 23, 1999, R.W. Johnson Pharmaceutical Research Institute stated that "the company would be willing now to provide the Agency with a written commitment of its promotional intention to avoid using the "Ultra" in Ultracet to suggest a "super acetaminophen."

PRODUCT INFORMATION
Ultracet consists of two ingredients, tramadol and acetaminophen. Tramadol is a centrally acting synthetic analgesic compound. The mode of action is not completely understood, but animal tests show that it binds to u-opioid receptors and inhibits the reuptake of norepinephrine and serotonin. Acetaminophen is another centrally acting analgesic. Although the exact site and mechanism of its analgesic action is not clearly defined, acetaminophen appears to produce analgesia by elevation of the pain threshold. The potential mechanism may involve the inhibition of the nitric oxide pathway mediated by a variety of neurotransmitter receptors including N-methyl-D-aspartate and Substance P. Ultracet is indicated for the management of [redacted] acute [redacted] pain. Racemic tramadol is rapidly and almost completely absorbed after oral

administration. The peak plasma concentrations of acetaminophen occur within one hour and are not affected by co-administration with tramadol. Tramadol is extensively metabolized after oral administration. The major metabolic pathways appear to be *N*- and *O*- demethylation and glucuronidation or sulfation in the liver. Approximately 30% of the dose is excreted in the urine as unchanged drug, whereas 60% of the dose is excreted as metabolites. Acetaminophen is primarily metabolized in the liver. In adults, the majority of acetaminophen is conjugated with glucuronic acid and, to a lesser extent, with sulfate. Plasma elimination half-lives of racemic tramadol and its metabolite are six and seven hours, respectively. The half-life of acetaminophen is about two to three hours in adults. The pharmacokinetics of tramadol/ acetaminophen combination in patients with renal or hepatic impairment have not been studied. However, the use of Ultracet is not recommended in patients with severe hepatic impairment because it is extensively metabolized in the liver. The usual dose is 1 to 2 tablets every 4 to 6 hours. It is supplied as 37.5 mg tramadol hydrochloride/ 325 mg acetaminophen tablets.

II. RISK ASSESSMENT

In order to predict the potential medication errors and to determine the degree of confusion of the proposed proprietary name, Ultracet, with other drug names, the medication error staff of OPDRA searched American Drug Index (42nd Edition), Drug Facts and Comparisons (1998 Edition), PDR (53rd Edition, 1999), Drug Product Reference File (DPRF), Electronic Orange Book, Micromedex online, and EES (Established Evaluation System) for possible sound-alike or look-alike names to approved and unapproved drug products. A focus group discussion was conducted to review all of the findings from the searches. In addition, OPDRA conducted studies of written and verbal analysis of the proposed proprietary name employing health practitioners within OPDRA to evaluate potential errors in handwriting and verbal communication of the name. This exercise was conducted to simulate an actual practice setting.

A. Study conducted within OPDRA

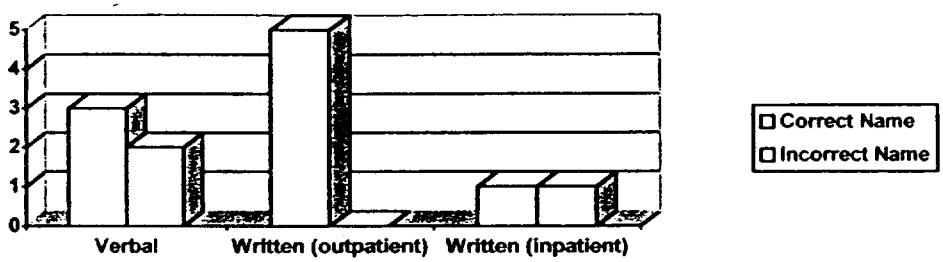
1) Methodology

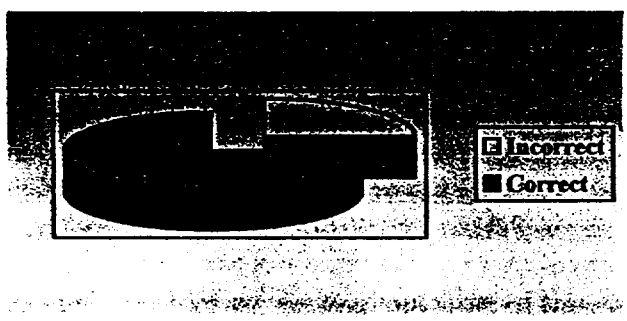
This study involved 18 health professionals comprised of pharmacists, physicians, and nurses within OPDRA to determine the degree of confusion of Ultracet with other drug names due to the similarity in handwriting and verbal pronunciation of the name. Random samples of either inpatient or outpatient written orders were delivered to the participating health professionals via e-mail. In addition, verbal orders via voice mail were sent to the participating health professionals for their review. After receiving the prescription orders, the participants sent their interpretations of the prescriptions vial e-mail to the medication error staff. After receiving the interpretations, the correct spelling of the proposed proprietary name was sent to the health professionals with a request for handwriting samples of the names. The medication error staff then reviewed the samples of the handwritten names.

2) Results

We received responses from twelve participants, nine of which correctly interpreted the proposed proprietary name, Ultracet. Five interpretations for verbal orders, five for outpatient written orders, and two for inpatient written orders were received. The results are as follows:

Ultracet





Incorrect names include: Ultralet, Ultraset, & Ultracette

B. Focus Group Findings

1) The proposed proprietary name, Ultracet, is similar to Ultracef, which is a tradename for cefadroxil. These two names differ only in the last letter of the name. Ultracef products were available as tablets, capsules, and powder for reconstitution [redacted] but these NDA's were withdrawn. On September 27, 1999, the last of the Ultracef products, the tablet formulation (NDA 62390), was withdrawn. Ultracef tablets were last distributed in 1990. However, the IND for Ultracef [redacted] is still in active status.

Although there is a similarity of the names between Ultracet and Ultracef, it is unlikely that Ultracet may be misconstrued as an antibiotic and confused for Ultracef since this antibiotic was withdrawn from the market.

2) Many products that contain acetaminophen as one of the ingredients have the stem, "cet", as part of the proprietary name. It is a familiar stem to many health

practitioners. Some examples include Fioricet, Roxicet, Hydrocet, Lorcet, Darvocet, and Percocet. Although the intention may have been to combine the association of both ingredients in the name, "cet" from acetaminophen and "Ultra" from Ultram, the acetaminophen component is more emphasized because the stem, "Ultra", is not exclusively associated with Ultram. The stem, "Ultra" is a known prefix to many proprietary names, including Ultravate, Ultralente, Ultrase, and Ultrabrom. However, there is insufficient evidence to object to the name, Ultracet, given that there are many proprietary names with the prefix, "Ultra", in the name.

C. Discussion

The results of the verbal and written analysis studies demonstrate that nine out of twelve participants correctly interpreted the proprietary name, Ultracet. Furthermore, the inaccurate interpretations of the proposed tradename did not overlap with any existing approved drug products, including Ultracef. Moreover, searches in available texts, databases, and the handwriting samples did not produce any significant new information to render Ultracet objectionable.

III. RECOMMENDATIONS

A. OPDRA has no objections to the use of the proprietary name, Ultracet.

B. The container labels and carton labeling were not available for possible interventions in minimizing medication errors.

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Lauren Lee, Pharm.D. at (301) 827-3243.

/S/ 11/12/99

Lauren Lee, Pharm.D.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

/S/ 11/12/99

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

HFD550
KONG

MEETING MINUTES

MEETING DATE: July 6, 2000 **TIME:**10:30 a.m. – 12p.m. **LOCATION:** CORP S400

NDA#: 21-123

Meeting Request Submission Date: June 8, 2000
Briefing Document Submission Date: June 22, 2000
Additional preparation documents: June 28, 2000

DRUG: Ultracet (tramadol HCl 37.5mg/acetaminophen 325 mg)

APPLICANT: The R. W. Johnson Pharmaceutical Research Institute

TYPE of MEETING: Special Guidance

FDA PARTICIPANTS:

Robert Delap, M.D., Ph.D.	Office Director, Office of Drug Evaluation V
Karen Midthun, M.D.	Division Director, DAAODP
Lourdes Villalba, M.D.	Medical Reviewer
Stan Lin, Ph.D.	Statistics Team Leader
Robert Osterberg, Ph.D., R.Ph.	Acting Pharmacology/Toxicology Team Leader
Yoon Kong, Pharm.D.	Project Manager
Barbara Gould	Project Manager

INDUSTRY PARTICIPANTS:

The R.W. Johnson Pharmaceutical Research Institute

Ravi K. Desiraju, Ph.D.	Vice President, Global Development
Robert A. Medve, M.D.	Director, Global Clinical Research and Development
Robert Wills, M.D.	Senior Vice-President Clinical Research and Development
Graham Burton, M.D.	Vice-President, Clinical Research and Development
Julia Wang, Ph.D.	Biostatistics
Gordon Pledger, Ph.D.	Biostatistics
Tracey Acker	Regulator Affairs
Jean O'Connor	Senior Director Regulatory Affairs
Peggy Ferrone	Principal Regulatory Affairs Scientist
Natasha Rogozenski	Assistant Director Regulatory Affairs

Ortho-McNeil Pharmaceuticals

Louis Ferrari	Group Product Director, Analgesics
Marc Kamin, M.D.	Senior Director, Clinical Investigations CNS

MEETING OBJECTIVES: To discuss issues cited in an approvable action letter issued and faxed on June 30, 2000.

BACKGROUND INFORMATION: On June 30, 2000, an approvable action letter was faxed to sponsor. Sponsor submitted briefing package on June 22, 2000, to discuss issues related to short-term management of acute pain [redacted] The sponsor submitted additional materials on June 28, 2000.

The sponsor opened the meeting by expressing their desire to resolve any scientific issues related to their NDA and by stating their belief that Ultracet was approvable for both acute [redacted] pain indications.

The sponsor emphasized the proven safety of both tramadol and acetaminophen and the common practice of "adding on drugs to baseline use of acetaminophen or NSAID". The sponsor described their product (Ultracet) as a "complementary product" in that it combines short-acting acetaminophen with long-acting tramadol.

In terms of pain management in general, the sponsor pointed out that there is a balance between benefits and adverse effects of a drug. Sponsor stated that the guiding principle of pain management is on an individual patient basis (individual dose titration of medication); which supports the flexibility in dosing and titration of 1-2 tabs q4-6 hours. The sponsor believes that their data supports acute [redacted] pain indications in the labeling of Ultracet.

DISCUSSION:

FDA indicated that the efficacy of a single Ultracet tablet (tramadol hydrochloride 37.5mg and acetaminophen 325-mg) has not been adequately studied and that sponsor would need to conduct a study to support the efficacy of a 1-tablet dose. Sponsor responded that they could conduct such a study (25-mg tramadol separated from placebo in one of their early, non-pivotal studies), but in their view, it would not add relevant information. Sponsor views the 1-tablet dose as adequate to treat acute pain based on their [redacted] studies.

FDA asked sponsor what gave them confidence that a single tablet dose of Ultram (tramadol 50 mg) is effective in acute pain, other than the dental pain model. According to the FDA, in the current NDA application, there is no compelling study with robust results, which indicate that a 25-mg tablet of tramadol alone provides pain relief. Moreover, study results of the 50-mg tramadol tablet in NDA 20-281 (Ultram), did not provide strong evidence to support efficacy of this dose. Sponsor stated that patients do take 1 tablet dose and that the use of 1 or 2 tablets was not out of context of treatment in acute pain indications. Sponsor noted that the information that FDA sought regarding the efficacy of a single Ultracet tablet might be located in the June 22 and 28, 2000, briefing packages submitted.

FDA pointed out that the additional data recently submitted by the sponsor (2 weeks prior to this meeting) appeared to be insufficient to support the efficacy of a 1-tablet dose of Ultracet, based on a preliminary review.

FDA indicated that the difficulty lies in how to extract information that supports the efficacy of a 1-tablet dose of Ultracet in the short-term management of acute pain in a post-surgical setting. FDA cited the following problematic aspects:

A second question posed to the sponsor was the issue of the efficacy of 2 tablets in other acute pain models, since the sponsor's second acute pain model (post-surgical orthopedic model) used a single dose of 3 tablets instead of 2 tablets of Ultracet. FDA agreed with the sponsor that each component (tramadol and acetaminophen) makes a contribution to the combination drug product, but the question still remains as to what dose of the combination drug product produces adequate efficacy.

FDA asked about sponsor's selection of dose. More specifically, FDA inquired about sponsor's rationale when they proposed the 3-tablet dose of Ultracet for the post-surgical orthopedic pain model. Sponsor stated that their selection of the 3-tablet dose (112.5 mg of tramadol and 975 mg of acetaminophen) was based on the data that a 100-mg dose of tramadol (Ultram) provided adequate efficacy in a surgical pain model.

Due to the lack of apparent evidence for the efficacy of 1 tablet and the lack of replicated evidence of the efficacy of 2 tablets in a second acute pain model, FDA recommended that sponsor should consider conducting a study in a non-dental pain model (e.g., 3-5 day study in a post-surgical orthopedic pain model) to evaluate the efficacy of these doses in a placebo-controlled study.

Sponsor indicated that such a study could be conducted , however, they voiced their disappointment with the division for the timing of doing such a study. Sponsor pointed out that 75 mg of tramadol separated from placebo in a post-surgical model and that 650-mg of acetaminophen is a fairly effective dose in terms of analgesic properties. FDA responded that adequate data to support this should be submitted.

Sponsor requested that FDA analyze the acute musculoskeletal pain information in the original Ultram (NDA 20-281) application. FDA stated that if the sponsor would like us to review these data, then they would need to resubmit to NDA 21-123 in a written and organized manner.

FDA suggested that a short-term multiple dose study should be performed in an acute pain model. Sponsor stated with confidence that a lower single dose of tramadol behaves well. Sponsor further indicated that they could provide data to support a 1-tablet dose.

Sponsor asked what the objective of a multiple dose study in an acute pain model would be. FDA noted that a dosing interval of q 4-6 hours appears reasonable (based on time to remedication), however, it is unclear whether a 1-tablet dose of Ultracet provides efficacy in any acute pain model and whether a 2-tablet dose of Ultracet provides efficacy in a non-dental acute pain model (e.g., post-orthopedic surgery).

Sponsor asked if FDA would consider labeling for 2 tablets of Ultracet as starting dose for acute pain and offered to study the 1-tablet dose, post-approval. FDA asked what the safety database is to support the use of 2 tablets q 4-6 hours. Sponsor countered that Ultracet is a combination of two commonly used drugs and that the 2-tablet dose (which contains tramadol 75 mg and acetaminophen 650 mg) is well within the therapeutic range recommended for the individual components.

FDA reminded sponsor that safety data should be procured per ICH guidelines to support the proposed clinical dose (if clinical recommended dose is 8 tablets per day, then need to evaluate safety data for these doses).

FDA acknowledged that there is experience with both the tramadol and acetaminophen components of a combination drug, however there are not sufficient data to support the long-term safety of the combination drug product at this juncture. FDA emphasized to the sponsor that per ICH guidelines, need to look at the upper end of dosing range to detect a 1% of adverse events (300 patients exposed for 6 months to drug, then 100 patients for a minimum of 1 year at the highest recommended dose).

FDA asked the sponsor to provide detailed information to indicate the number of patients who had received 6, 7, and 8 tablets per day by the number of days exposed, as this information had not been provided in the NDA.

Sponsor recognized FDA's concern regarding labeling of their combination product and indicated that they would return with information required for approval of drug product. FDA concurred with this strategy and pointed out that an acute pain indication for Ultracet would be more viable [redacted] indication given the information reviewed. [redacted]

ACTION ITEMS:

1. Sponsor will conduct studies for short term management of acute pain [e.g., effect of a single tablet dose; utility of the 2 tablet dose in the treatment of non-dental acute pain conditions (e.g., post –orthopedic surgery); multiple dose effect; adequate safety database based on dosing recommendation established].

[redacted]

3. FDA will convey minutes to sponsor within 30 days of sponsor meeting.

/S/ 8-29-00
Yoon Kong, Pharm.D.
Project Manager

Concur: /S/ 8-29-00
Karen Midthun, M.D.
Division Director, DAAODP

Addendum:

Follow-up meeting to discuss pending [redacted] issues scheduled for September 7, 2000.

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

HFD 550
KONG

TELECON MINUTES

TELECON DATE: March 1, 2000 **TIME:** 1:30 p.m.-2:00 **LOCATION:** CORP N368

NDA #: 21-123

Telecon Request Submission Date: February 29, 2000
(Meeting requested by sponsor)
Date Sponsor Requested:
(if beyond the 60 or 75 days) n/a
Briefing Document Submission Date: n/a
Additional preparation documents: n/a

DRUG: Ultracet (tramadol hydrochloride/acetaminophen)

APPLICANT: The R.W. Johnson Pharmaceutical Research Institute

TYPE of TELECON: General Information

FDA PARTICIPANTS:

Chang Lee, M.D.	Medical Reviewer
Yoon Kong, Pharm.D.	Project Manager

INDUSTRY PARTICIPANTS:

Robert A. Medve, M.D.	Director, Global Clinical Research and Development
Julia Wang, Ph.D.	Statistician
Peggy Ferone	Principal Regulatory Affairs Scientist
Natasha Rogozenski	Assistant Director Regulatory Affairs

TELECON OBJECTIVES: The sponsor requested this teleconference for clarification of the medical reviewer's request for additional information on safety anaylses.

BACKGROUND INFORMATION: Per request of the medical reviewer, a request for additional safety analyses was faxed to the sponsor on January 25, 2000. In the request, the medical reviewer requested the following from the sponsor:

1. Inclusion of an analysis of "Number of Patients Receiving New Drug According to Mean Daily Dose and Duration of Therapy in Phase 2-3 Studies" (Table 1).

TABLE 1

Duration (Days)	TRAM/APAP < 4 TABLETS/DAY	TRAM/APAP 4 - 7 TABLETS/DAY	TRAM/APAP > 7 TABLETS/DAY	Total	(%)
Single Dose					
Any exposure					
≥ 7					
≥ 15					
≥ 30					
≥ 60					
≥ 90					
≥ 180					
≥ 270					
≥ 360					
≥ 720					
Total					
(%)					

2. Addition of another column (variable: dose) in the "Serious Adverse Event Listing Table". The added column should include the dose being adminstered (mg/day) at the time the event occurred.
3. Inclusion of a "Summary of Adverse Event Dropout Listing" (Table 2).

TABLE 2

Dropout Profile: Incidence of Dropout by Treatment Group and Reason for Phase 2-3 Studies with New Drug Cutoff Date:			
Reason for Dropout	Treatment Groups		
	New Drug N=	Placebo	Active Control N=
Lack of Efficacy	%	%	%
Adverse Event	%	%	%
Lost to Follow Up	%	%	%
Total Dropouts	%	%	%

TABLE 3

[redacted]

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

1. In the "Serious Adverse Event Listing Table", can the sponsor use the dose being administered as an average per week rather than mg/day? Depending on the study, there may not be an administration of proposed drug on specific days.

   Yes, provided that this is noted by the sponsor in the table.

2. Should the column header for Table 2 be "Dropout Profile: Incidence of ALL Dropout....."?

   Yes.

[redacted]

The medical reviewer for the Division recommended the use of a dose-response relationship (i.e. patients < 3 months, patients> 3-6 months, patients>6 months)

ACTION ITEMS:

1. The sponsor will provide responses to medical officer's request for additional safety analyses which would include mean daily dose and duration of therapy, an adverse event listing, summary of adverse event dropouts, and an assessment of dose-response experience of frequently reported adverse events.

2. FDA will convey minutes to the R.W. Johnson Pharmaceutical Research Institute within 30 days of teleconference date.

/S/

Yoon Kong, Pharm.D.
Project Manager

Concur:

/S/

Chang Lee, M.D.
Medical Reviewer

a.c.D
3/3/00

cc: NDA # 21-123
HFD-550/Div File
HFD-550/C. Lee
HFD-550/LVaccari
HFD-550/Kong

Drafted by: YJK/3-3-00
Initialed by: Chang Lee/
Leslie Vaccari/

Final:

TELECON MINUTES

TELECON MINUTES

TELECON DATE: June 8, 2000 **TIME:** 10:00 a.m.- 10:45 a.m. **LOCATION:** CORP S400

NDA #: 21-123

Telecon Request Date: June 8, 2000
(Meeting requested by FDA)
Briefing Document Submission Date: n/a
Additional preparation documents: n/a

DRUG: Ultracet (tramadol HCl 37.5 mg/ acetaminophen 325 mg)

APPLICANT: The R. W. Johnson Pharmaceutical Research Institute

TYPE of TELECON: Special Information

FDA PARTICIPANTS:

Karen Midthun, M.D.	Division Director, DAAODP
Chang Lee, M.D., Ph.D.	Medical Reviewer
Stan Lin, Ph.D.	Statistics Team Leader
Bart Ho, Ph.D.	Chemistry Reviewer
Dennis Bashaw, Pharm.D.	Pharmacokinetics Team Leader
Robert Osterberg, Ph.D., R.Ph.	Pharmacology/ Toxicology Team Leader
Yoon Kong, Pharm.D.	Project Manager

INDUSTRY PARTICIPANTS:

Michael Blank, Ph.D.	Director, Global Development
Andrew Chow, Ph.D.	Research Fellow, Clinical Drug Metabolism
Ellen Codd, M.S.	Principal Scientist, Drug Discovery
Timothy Coogan, Ph.D.	Principal Scientist, Drug Safety Evaluation
Ravi Desiraju, Ph.D.	Global Product Leader
Louis Ferrari	Director, Marketing, Analgesics
Peggy Ferrone	Principal Regulatory Affairs Scientist
Irwin Gibbs, Ph.D.	Chemistry, Manufacturing and Controls Team Leader
Marc Kamin, M.D.	Senior Director, Clinical Investigations-CNS
Stephen Klincewicz, D.O., M.P.H., JD	Global Safety Officer, Global Safety and Pharmacovigilance
Sam Liao, Ph.D.	Consultant, Clinical Drug Metabolism
Robert Medve, M.D.	Director, Global Clinical Research and Development

Ramchandra Nayak, Ph.D.	Director, Clinical Drug Metabolism
Jean O'Connor	Senior Director, Regulatory Affairs
Natasha Rogozenski	Assistant Director, Regulatory Affairs
Anthony Streeter, Ph.D.	Research Fellow, Preclinical Drug Metabolism
Julia Wang, Ph.D.	Senior Biostatistician, Clinical Biostatistics
Philip Lane, Ph.D.	Director, New Product Development

TELECON OBJECTIVES: FDA requested this teleconference to inform the sponsor that the reviews of their NDA application (NDA 21-123) had been completed and that some problematic issues regarding the clinical data had been identified.

BACKGROUND INFORMATION: Sponsor submitted application on August 31, 1999, received by FDA on September 1, 1999. With the upcoming ten-month review date of July 1, 2000, the FDA completed its review of NDA submission and wished to notify sponsor that certain clinical deficiencies had been identified prior to issuance of action letter.

ISSUES for DISCUSSION:

FDA noted that the reviews of NDA 21-123 had been completed. FDA conveyed to the sponsor that there were no pharmacology/toxicology or pharmacokinetic issues. The only outstanding chemistry issue was that a site in Germany had not been inspected. Sponsor confirmed that this site had been scheduled for inspection; they stated that the date was July 14, 2000.

FDA noted, however, that there are clinical deficiencies and outlined them as follows:

ACUTE PAIN INDICATION

Major issues with regard to the acute pain indication:

- Dosing Recommendations

  It is unclear how to formulate dosing recommendations given that no multiple (repeat) dosing studies were performed by the sponsor in acute pain conditions; there was no information on dose response provided. Also, no data for use of 1 tablet for treatment of acute pain was provided.

- Efficacy

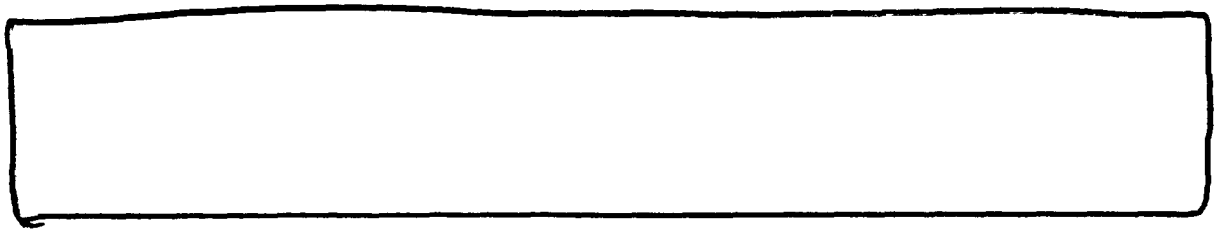
  With respect to efficacy, FDA indicated that the contribution of each component of the combination product (tramadol hydrochloride 37.5 mg/ acetaminophen 325-mg) to the analgesic effect of the drug had been demonstrated for the 2 tablet dose in the dental pain model. However, it was unknown whether the proposed dose of 2 tablets would provide

efficacy vs. placebo in non-dental acute pain conditions (e.g., post-surgical), because a 3 tablet dose had been used in the post-surgical studies.

- Safety

The highest recommended dose proposed by the sponsor is 8 tablets/day. Only 156 patients were exposed to ≥ 8 tablets/day for greater than 7 days; hence, FDA noted that this patient exposure was not sufficient to support short-term use. There should be safety data on at least 300 patients who have been exposed to the maximum recommended dose for a duration of 10 or more days to support the acute pain indication.

Also, safety data should be analyzed by age (< 65 years and ≥ 65 years).



DISCUSSION FOLLOWING FDA COMMENTS:

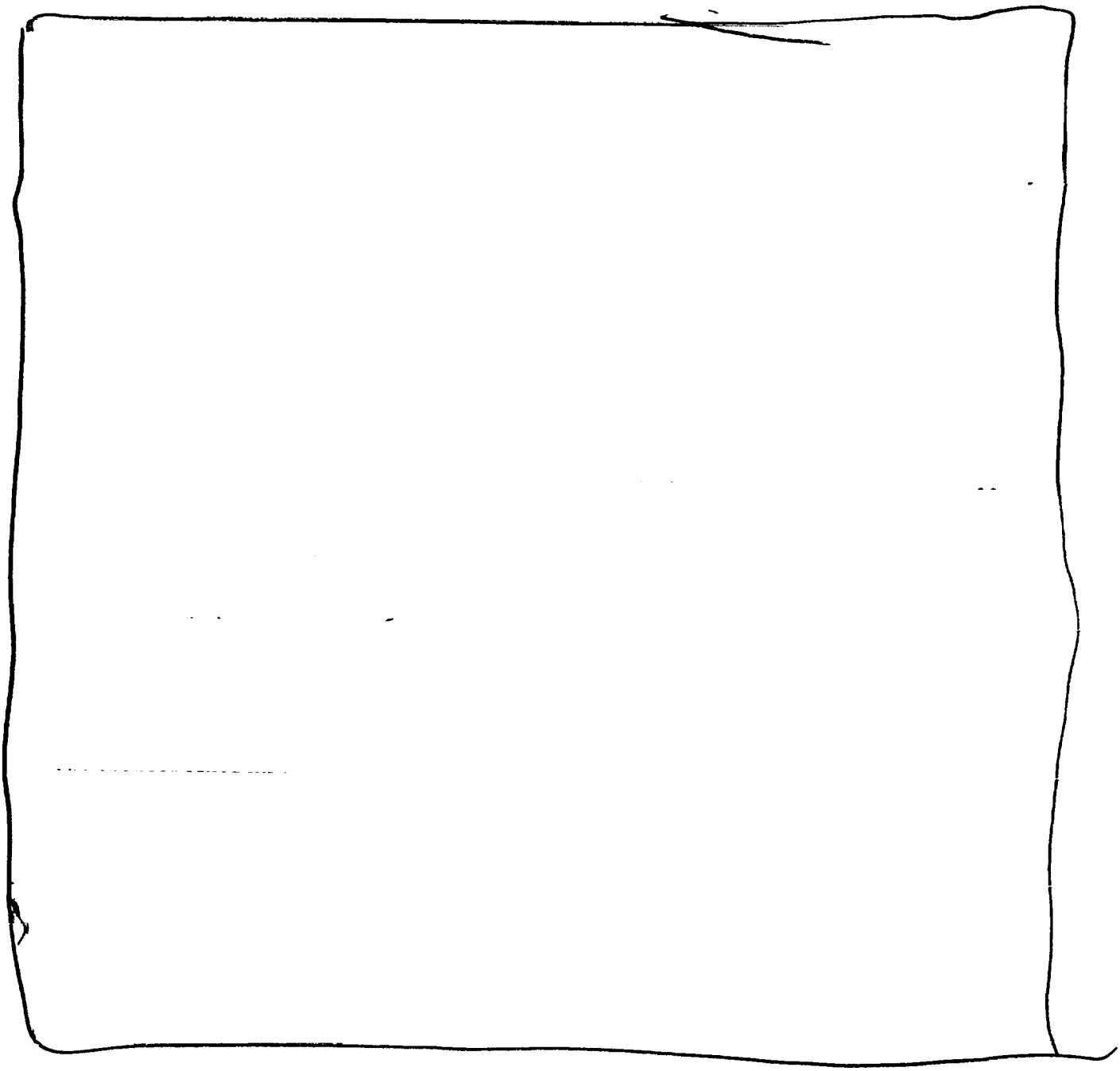
ACUTE PAIN

With regard to efficacy, the sponsor asked if the issue was that the combination drug product did not separate from its components or from placebo. FDA clarified that the data supported that the combination product had an advantage over each of its components alone. FDA emphasized that the real clinical issue was insufficient data to support the proposed dosing recommendation.

The sponsor questioned the need for safety data in 300 patients at the highest recommended dose, given that both components of the combination product are approved. FDA noted that the combination was a new product and thus, required sufficient safety data in support of its use. With regard to the safety database, the sponsor noted that the Division had previously indicated that meeting ICH guidelines for safety was sufficient, and the sponsor had fulfilled these guidelines. FDA stated that it was unclear whether the ICH guidelines had been met because the data presented were not adequate to determine what the clinically recommended dose should be.

Further, the sponsor inquired if the FDA could recommend a proper dosage for the combination drug product based on the current information. FDA noted that in the dental pain model, a 2-tablet single dose was efficacious relative to placebo. In the post-surgical pain studies, a 3-tablet single dose was efficacious relative to placebo. However, it was unclear what the subsequent dosage recommendations should be for continued pain relief in the acute pain model. Also, there were insufficient data to support that a 1-tablet dose would be efficacious in an acute pain

condition or that a 2-tablet dose would be efficacious in a non-dental acute pain condition. The sponsor stated that they could not address these issues at this juncture.



ACTION ITEMS:

ACTION ITEMS:

1. FDA will convey meeting minutes to R.W. Johnson within 30 days of teleconference.

/S/ 6-27-00

Yoon Kong, Pharm.D.
Project Manager

Concur: /S/ 6-27-00

Karen Midthun, M.D.
Division Director, DAAODP

TELECON MINUTES

TELECON DATE: June 12, 2000 **TIME:** 10:30 a.m.-10:45 a.m. **LOCATION:** 550 Window Conference Rm.

NDA # 21-123

Telecon Request Date: June 12, 2000
Briefing Document Submission Date: n/a
Additional preparation documents: n/a

DRUG: Ultracet (tramadol HCl 37.5 mg/ acetaminophen 325 mg)

APPLICANT: The R. W. Johnson Pharmaceutical Research Institute

TYPE of TELECON: General Information

FDA PARTICIPANTS:

Karen Midthun, M.D.	Division Director, DAAODP
Yoon Kong, Pharm.D.	Project Manager

INDUSTRY PARTICIPANTS:

Jean O'Connor	Senior Director Regulatory Affairs

TELECON OBJECTIVES: To establish correspondence between Ms. O'Connor and Dr. Midthun in the follow-up to the June 8, 2000, teleconference.

ISSUES for DISCUSSION:

Ms. O'Connor thanked Dr. Midthun and the Division for conveying the outcome of reviews for NDA 21-123 (Ultracet®) during the June 8, 2000 teleconference. Ms. O'Connor informed Dr. Midthun that the sponsor was composing a formal meeting request letter to the FDA to discuss outstanding clinical issues raised during the June 8, 2000 teleconference (refer to June 8, 2000 TCON minutes) for Ultracet®. The sponsor requested that FDA schedule this meeting as soon as possible with the presence of Dr. Delap at such a meeting.

Dr. Midthun noted that the sponsor's requested meeting would be arranged by the Project Manager in an expedient and timely manner such that all the necessary FDA participants would be able to attend. It was indicated that the Project Manager would notify sponsor with a suitable date within the next few days.

ACTION ITEMS:

1. FDA will notify sponsor with a date for follow-up meeting to June 8th teleconference.

2. FDA will convey teleconference meeting minutes to R. W. Johnson within 30 days.

/S/ 6-27-00
Yoon Kong, Pharm.D.
Project Manager

Concur: /S/ 6-27-00
Karen Midthun, M.D.
Division Director, DAAODP

TELECON MINUTES

TELECON DATE: June 23, 2000 **TIME:** 9:00 a.m.

NDA #: 21-123 **Telecon Request Date:** June 22, 2000

DRUG: Ultracet (tramadol 37.5 mg/acetaminophen tablets 325 mg) Tablets

APPLICANT: The R.W. Johnson Pharmaceutical Research Institute

TYPE of TELECON:

FDA PARTICIPANTS:

Robert Delap, M.D., Ph.D.	Office Director, Office of Drug Evaluation V
Mary Jane Walling	Associate Director for Regulatory Policy, Office of Drug Evaluation V /S/ 6/29/00

INDUSTRY PARTICIPANTS:

Dr. Graham Burton	Vice President Global Clinical Research and Regulatory Affairs

DISCUSSION:

Dr. Burton placed the call to discuss a process issue. He was surprised at the timing of the meeting to discuss scientific issues scheduled after the 10 month PDUFA action date. He indicated that he was surprised that the division's conclusion was NA after reviewing the data. He stated that RWJ wishes to negotiate in a good spirit and maintain a partnership. He felt the deficiencies could be handled Phase 4 and said they would abide by any commitments to avoid an NA.

Dr. DeLap said that he appreciated communication about process issues, but that since this was not an NME the divisions handle the review, identify the deficiencies while focusing on the data to demonstrate safety and efficacy and the ability to label a drug, and then issue an action. When the action is other than AP, it is usual to complete the action and then discuss the next steps necessary to bring the application into approval status. He encourages the divisions to let the sponsors know about the magnitude and nature of the deficiencies before sending the letter.

He further stated that he would look into the this before participating in the tele-con scheduled for June 27, but that he can't commit to extending the clock to 12 months. He stated that we had

good interactions with RWJ over time and Dr. Burton allowed as how the company had other products in the pipeline and wanted to continue the partnership without rancor.

The call was cordial.

ACTION ITEMS:

1. FDA will convey minutes to sponsor within 30 days of teleconference.

/S/

Mary Jane Walling
Associate Director of Regulatory Affairs, ODE V

Concur: /S/ 6/29/00

Robert Delap, M.D., Ph.D.
Director, ODE V

TELECON MINUTES

TELECON DATE: June 27, 2000 **TIME:** 10: 30 a.m. – 11:15 a.m.

NDA #: 21-123 **Telecon Request Submission Date:** June 19, 2000
Briefing Document Submission Date: n/a
Additional preparation documents: n/a

DRUG: Ultracet (tramadol HCl 37.5 mg/ acetaminophen 325 mg)

APPLICANT: The R. W. Johnson Pharmaceutical Research Institute

TYPE of TELECON: Special Guidance

FDA PARTICIPANTS:

Robert Delap, M.D., Ph.D.	Office Director, Office of Drug Evaluation V
Karen Midthun, M.D.	Division Director, DAAODP
Yoon Kong, Pharm.D.	Project Manager
Lourdes Villalba, M.D.	Medical Officer

INDUSTRY PARTICIPANTS:

Robert Medve, M.D.	Director, Global Clinical Research and
Dr. Graham Burton	Vice President Global Clinical Research and Regulatory Affairs
Peggy Ferrone	Principal Regulatory Affairs Scientist
Natasha Rogozenski	Assistant Director, Regulatory Affairs Development

TELECON OBJECTIVES: To discuss issues raised by the sponsor in their written request for a teleconference with the FDA, submitted on June 19, 2000 and received on June 21, 2000. Sponsor indicated in this above-mentioned missive their purpose it to obtain assurance from the Agency that the action letter will not be issued prior to July 6, 2000, meeting and to reach a mutual agreement on extending the 10-month PDUFA date in order to resolve issues raised in the June 8, 2000, teleconference.

BACKGROUND INFORMATION: Please refer to June 8 and 12, 2000 teleconference meeting minutes.

DISCUSSION and DECISIONS REACHED:

The sponsor began by informing FDA of the teleconference that occurred between Dr. Burton and Dr. Delap on June 23, 2000. The sponsor noted that from that discussion, they understood that scientific meetings are conducted following an issuance of an action letter. However in light of the significant procedural and scientific issues raised in their briefing meeting packaged dated on June 22, 2000 (for July 6, 2000 meeting), sponsor requests that an extension on the review clock from the 10-month (July 1, 2000) to 12-month (September 1, 2000) should be seriously considered.

FDA acknowledged receipt of briefing meeting package dated June 22, 2000. FDA informed sponsor that we intend to take a preliminary review this package to determine if information provided in this package addresses deficiencies conveyed to sponsor on June 8, 2000 teleconference. If indeed, this information presented suffices to address deficiencies, then this would warrant an extension of the review time clock to 12-month PDUFA date (September 1, 2000) for adequate review of application. On the other hand, if this does not provide any new substantial information to the completed reviews, then FDA will issue an action letter by 10-month PDUFA date.

Sponsor inquired if the action letter would be issued following the July 6, 2000 meeting, given the preliminary review of briefing packaged dated June 22, 2000. Again, FDA reiterated that based on the preliminary review of the briefing package dated June 22, 2000, a decision would be made to extend the review clock or issue an action letter per the 10-month PDUFA date (July 1, 2000).

Sponsor asked what the time period for preliminary review of briefing package dated June 22, 2000. FDA replied that it would take a few days.

Sponsor expressed that their review of historical relationship with the FDA led them to believe that this application would be approvable. Sponsor stated their view that the FDA was requesting a completely new drug developmental plan. Sponsor indicated that their comments on procedural issues are delineated in briefing package dated June 22, 2000. Sponsor asked whether the FDA had any comments about the procedural issues; the sponsor stated that they understood that fileability did not mean approvability. FDA noted that the desire, once an application is filed for FDA review, is to ultimately find it an approvable application; however, the outcome depends on the review. FDA indicated that the process and procedural issues can be discussed (with part of the issue being that one can learn how things can be done differently).

FDA noted that in order to label the product, the following issues need to be further addressed: the appropriate dose for acute pain, the issue of adequacy of safety exposure [redacted] The sponsor inquired if the plan would be for them to address these issues after an action letter was issued, which could possibly be a non-approvable action. FDA noted that it

would complete a preliminary review of the response that the sponsor had submitted on June 22, 2000 and subsequently, take this into consideration.

The sponsor stated their view that the information being requested by the FDA is very different from the clinical development plan that was conducted. FDA noted that we would not characterize the issues to be addressed as reflecting an entirely different clinical program (since there seems to be credibility to what sponsor has submitted thus far in application); the question is how to sufficiently address the gaps in knowledge that have been identified.

FDA reassured sponsor that we would preliminary review briefing package dated June 22, 2000 and would have further contact to inform sponsor what action will be taken.

Sponsor encouraged FDA to refer to Attachment #3 (June 22, 2000 briefing package) since it chronicled all of the interactions with FDA on this combination drug product. Sponsor noted that they were very responsive to FDA's requests in the past and felt that they had been let down. FDA stated that unfortunately, communication issues do arise, and sometimes FDA finds outstanding issues toward the end of the review process. FDA attempts to anticipate in advance gaps in knowledge that will need to be addressed by the sponsor. Occasionally, the questions posed by the sponsor are not as focused and directed as they ought to be during the drug development process.

Sponsor once again asked the FDA to review the June 22, 2000, submission and requested that they be contacted later in the week. FDA reemphasized that a preliminarily review of this package would be conducted and we would contact the sponsor before the end of the week.

FDA summarized list of concerns regarding the labeling of sponsor's combination drug product as it currently stands most notably: appropriate dose for acute pain (dental and non-dental pain models), safety exposure issues raised [redacted]

Sponsor inquired if they could potentially receive a non-approvable action letter. FDA noted that this could be the case, however, the information provided in the June 22, 2000, package would be considered in the action taken.

ACTION ITEMS:

1. FDA will communicate with the sponsor before the 10-month action due date of July 1, 2000.

2. FDA will convey minutes to sponsor within 30 days of teleconference.

/S/ 7-3-00
Yoon Kong, Pharm.D.
Project Manager

Concur: /S/ 7-3-00
Karen Midthun, M.D.
Division Director, DAAODP

TELECON MINUTES

TELECON DATE: June 29, 2000 **TIME:** 5:30 p.m.-5:45 p.m. **LOCATION:** 550 Window Conference Rm.

NDA # 21-123

Telecon Request Date: June 27, 2000
Briefing Document Submission Date: June 22, 2000
Additional preparation documents: n/a

DRUG: Ultracet (tramadol HCl 37.5 mg/ acetaminophen 325 mg)

APPLICANT: The R. W. Johnson Pharmaceutical Research Institute

TYPE of TELECON: Special Guidance

FDA PARTICIPANTS:

Robert Delap, M.D., Ph.D.	Office Director, Office of Drug Evaluation V
Karen Midthun, M.D.	Division Director, DAAODP
Yoon Kong, Pharm.D.	Project Manager
Barbara Gould	Project Manager

INDUSTRY PARTICIPANTS:

Robert Medve, M.D.	Director, Global Clinical Research and
Dr. Graham Burton	Vice President Global Clinical Research and Regulatory Affairs
Jean O'Connor	Senior Director Regulatory Affairs
Natasha Rogozenski	Assistant Director, Regulatory Affairs Development

TELECON OBJECTIVES: To inform sponsor of action on our review of application upon consideration of preliminary review of meeting package dated June 22, 2000.

BACKGROUND INFORMATION: See teleconference meeting meetings for June 8, 12, 26 and 27, 2000.

DISCUSSION:

FDA informed sponsor that upon consideration of preliminary review of the June 22 package, FDA did not feel that this provided sufficient information which would result in approval of application. However, based on the overall content of the application, FDA has decided to issue an approvable letter by 10-month PDUFA date of July 1, 2000.

Sponsor inquired if meeting scheduled for July 7, 2000 would still be appropriate. FDA advised sponsor that in light of outstanding clinical issues which need to be addressed for this application to be approved, such a meeting should still be conducted.

FDA further emphasized that the titling of the action letter is approvable and thus, does not mean final approval of application.

ACTION ITEMS:

1. FDA will convey minutes to sponsor within 30 days of teleconference.

/S/ 7-3-00
Yoon Kong, Pharm.D.
Project Manager

Concur: /S/ 7-3-00
Karen Midthun, M.D.
Division Director, DAAODP

RECORD OF A TELE-CON

DATE: August 3, 2001

PARTICIPANTS: MJ Walling and L. Villalba/FDA and Ferrone, Huff, Wang, Ravi and Medry/RWJ

SUBJECT: NDA 20-281

We asked for clarification on the geriatric ADE numbers in the proposed label; the number used to calculate the dropouts due to GI and body as whole events.

RWJ responded that the number s are based on numbers of patients not numbers of events

DATE: Aug. 7, 2001

PARTICIPANTS: MJ Walling and N. Rogozenski/Ortho RWJ

SUBJECT: Ultram label NDA 20-281

We asked for breakdown of ADEs by age as follows- 65, and.= 65 instead of 65-74, .75, and .=65.

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE: August 15, 2001

APPLICATION NUMBER: NDA 21-123 Ultracet (tramadol 37.5 mg/acetaminophen 325 mg) Tablet

BETWEEN:

Name:	Natasha Rogozenski	Director, Regulatory Affairs
	Douglas R. Hough, MD	Senior Director, Global Clinical Research & Development
	Robert Medve, MD	Senior Scientist, Drug Metabolism
	Norman Rosenthal, MD	Director, Clinical Research Diabetes, Metabolism, & Neuroscience
	Julia Wang, PhD	Principal Biostatistician, Clinical Biostatistics

Representing: The R.W. Johnson Pharmaceutical Research Institute

AND

Name:	Lawrence Goldkind, MD	Deputy Division Director
	Lourdes Villalba, MD	Medical Reviewer
	Barbara Gould,	Project Manager

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

SUBJECT: Labeling Negotiations

We had 3 issues for discussion:

1. **PK- absorption: inclusion of "rapid".**
   Regarding the PK issue, the term "rapid" is subjective and does not add to the pharmacokinetic descriptions.

   CONCLUSION: Sponsor accepted.

2. **Clinical study section: inclusion of "The onset of pain relief was consistently less than 30 min".**
   Median time to perceptible pain relief is one of the parameters used to determine the efficacy profile of an analgesic. It is a very valuable parameter only in the context of a particular study, relative to placebo and the active comparator.

   - TPPR does not give the complete picture. It is subject to misinterpretation. It may imply that all patients improved within 30 min, when some patients had no pain relief at all. Median time to meaningful pain relief, mean time to pain relief, and other endpoints may be of equal importance.

- Other studies may have a completely different population, with different demographics or different pain intensity baseline. As noted yesterday in the T-con, the dental pain used ibuprofen as comparator. Ibuprofen and placebo may behave differently in different studies.

- The Divisions guidance for required onset of action of an acute analgesic is within 1 hour. Labeling beyond this is not currently considered valuable for labeling.

CONCLUSION: The sponsor agreed to "the onset of action was less than one hour".

3. Drug interaction- carbamazepine section (switch of order of carbamazepine and ULTRACET).

CONCLUSION: The sponsor agreed to switch order of carbamazepine and ULTRACET.

/S/

Lawrence Goldkind
Deputy Division Director

From: Villalba, Lourdes
Sent: Monday, July 30, 2001 12:59 PM
To: Klein, Michael
Cc: Leiderman, Deborah; Calderon, Silvia N; Goldkind, Lawrence; Walling, Maryjane; Bonnel, Renan A
Subject: ULTRAM/ULTRACET

Mike:
Thank you for your consult on Ultracet recently submitted to DFS.
I am working on our response to the sponsor's proposed label for ULTRAM submitted by fax on July 25, in response to our request for labeling changes. (We are not going to negotiate the ULTRACET label until the sponsor and the Agency agree with the ULTRAM label).

I have incorporated the cross reference to the DRUG abuse section in the labor and delivery section but I don't think we have a clear report of dependence in a lactating infant (Renan: do you remember any case?).

I believe the risk of abuse in adolescents may be a significant problem (similarly to what happened with oxycontin). However, I only know of two very incomplete post-marketing reports of this kind. Renan has tried to get additional information without success. I am not sure these reports raise the level of concern to the point to have a separate statement of risk for this age population.

Questions:

1. Are there other products such as oxycontin, propoxyphen, morphine or other opioids that mention adolescents specifically in their label?

2. If that is the case, could you suggest specific wording similar to those labels that we could ask RWJ to include at this time of negotiation?

Thank you

Lourdes

M E M O R A N D U M

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

Date: July 26, 2001

To: Jonca Bull, M.D.
Acting Director, Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products (HFD-550)

Through: Deborah B. Leiderman, M.D., M.A.
Director, Controlled Substance Staff (HFD-009)

From: Michael Klein, Ph.D.
Controlled Substance Staff (HFD-009)

Subject: Controlled Substance Staff Consultation:
NDA 21-123 ULTRACET (Combination tablet of Tramadol hydrochloride 37.5 mg and Acetaminophen 325 mg)
Sponsor: R. W. Johnson Pharmaceutical Research Institute
Labeling Review (Class I Resubmission)
Date of Resubmission: June 14, 2001

Background

The Division of Analgesic, Anti-Inflammatory, and Ophthalmologic Drug Products (HFD-550) requested comments from the Controlled Substance Staff (CSS) on the revised product Draft Labeling for ULTRACET, which was submitted in response to the Agency's Approvable Letter of May 15, 2001.

CSS had reviewed the abuse liability assessment package of the NDA submitted on August 31, 1999, which consisted of studies with the combination product as well as reports of abuse of the single entity tramadol product (ULTRAM).

The sponsor has accepted most of the FDA proposals. However, an additional warning regarding the potential abuse of ULTRACET is recommended and discussed below.

Conclusions and Recommendations

1. Reports of abuse and dependence by non-patients as well as patients have been received from the sponsor. **Recent reports include abuse of tramadol by minors (ages 13 to 16 years). This needs to be clearly identified in the section on DRUG ABUSE AND DEPENDENCE**. Health care providers need to be warned of the

possibility of abuse of the product for its opioid-like effects particularly by adolescents who are likely to experiment with the drug for recreational purposes. The sponsor's proposed new language fails to incorporate this. As such, the sponsor's recommended changes to the **WARNINGS** section on **Physical Dependence and Abuse** and the **DRUG ABUSE AND DEPENDENCE** section does not convey the potential abuse problems that have been documented and should not be accepted.

2. Under **Labor and Delivery and Nursing Mothers** there should be cross-reference to the section on **DRUG ABUSE AND DEPENDENCE**, as dependence of neonates on tramadol has been reported.
3. Remaining changes including those dealing with overdose are adequate with respect to tramadol. Most of the sponsor's recommended revisions concern the ingredient, acetaminophen, which was not the focus of the present review.

CC: Original NDA 21-123
HFD-550/ J Bull/ L Goldkind/ C Fang/ ML Villalba/ Y Koon
HFD-170/ D Leiderman/ M Klein/ C Moody/ S Calderon/ D Locklear

MEMORANDUM

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

Date: November 27, 2000

To: Acting Director, Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products (HFD-550)

Through: Deborah B. Leiderman, MD, MA
Director, Controlled Substance Staff (HFD-009)

From: Ann-Kathryn Yelovich, MD and
Michael Klein, Ph.D.
Controlled Substance Staff (HFD-009)

Subject: NDA #21-123 (Pediatric Consult related to abuse)
Tramadol Hydrochloride/ Acetaminophen Tablets (ULTRACET®)

BACKGROUND.

This consult was requested for the pediatric team to obtain information regarding the potential for abuse of ULTRACET in the pediatric population. The following are points that we think the pediatric team may want to consider or may have already considered. After the points are presented, some of them will be discussed in more detail.

SUGGESTIONS.

1. In an adult, there is a high likelihood of dependence developing after the patient has taken an opiate for 10-14 days. Because the protocol will include some children who will be taking ULTRACET for at least this length of time, it is recommended that the study plan include a taper of the ULTRACET in at least these patients. Because pharmacokinetic differences may affect the length of time it takes for a patient to become dependent, all patients should be monitored for signs and symptoms of withdrawal.

2. It is recommended that the following points should be discussed with parents (and patients, if appropriate).

    a. The opiate-like nature of tramadol and the risk of abuse and dependence.
    b. The risk of serotonin syndrome.
    c. The following statements in the label:
        i. "ULTRAM (tramadol) should not be used in opioid dependent patients."

ii. "ULTRAM has been shown to reinitiate physical dependence in some patients that have been previously dependent on other opioids." (1)
iii. "In patients with a tendency to drug abuse, a history of drug dependence, or (who) are chronically using opioids, treatment with ULTRAM is not recommended." (2)

3. The safety assessment should include monitoring all children for signs and symptoms of intoxication and withdrawal.

4. Caution should be used when administering ULTRACET to patients with psychiatric disorders.

5. A contract might be helpful if it is decided to administer ULTRACET to a patient with a history of substance abuse.

6. Some children have experienced acetaminophen toxicity while receiving normal doses of the drug. Acetaminophen levels and liver function tests could be done as part of the safety assessment. If ULTRACET is abused, there would be a greater risk for acetaminophen toxicity.

DISCUSSION.

1. Various opiate tapering schedules have been used. One article described a 40 year old female who used tramadol for 7 weeks. After the tramadol was discontinued she decided to restart it because of withdrawal symptoms. The dose was progressively decreased and discontinued after 3 weeks. The woman tolerated the taper well (3).

A second case report involved a 46 year old female whose history was significant for previous alcohol and opiate dependence. She admitted to using up to thirty 50 mg tablets of tramadol daily and to abusing it for one year. Two 10 mg doses of methadone relieved her symptoms. The dose was decreased by 2.5 mg per day over 8 days. The patient tolerated this dose reduction well (4).

Goodman & Gilman note that in adults the dose of an opioid can be reduced by 50% every several days and then eventually stopped to avoid withdrawal (5).

2. Serotonin syndrome has been reported when SSRIs and tramadol were used simultaneously. This syndrome is rare but potentially fatal (6). It occurs most often when an SSRI is given with a monoamine oxidase inhibitor and also has occurred when venlafaxine was given with a monoamine oxidase inhibitor (7).

3. DSM-IV-TR Diagnostic Criteria for Opioid Intoxication.

A. Recent use of an opioid.

B. Clinically significant maladaptive behavioral or psychological changes (e.g., initial euphoria followed by apathy, dysphoria, psychomotor agitation or retardation, impaired judgment, or impaired social or occupational functioning) that developed during, or shortly after, opioid use.
C. Pupillary constriction (or pupillary dilation due to anoxia from severe overdose) and one (or more) of the following signs, developing during, or shortly after, opioid use:
    a. Drowsiness or coma
    b. Slurred speech
    c. Impairment in attention or memory
D. The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder.

Specify if: with perceptual disturbances (8), such as hallucinations or visual, auditory, or tactile illusions.

DSM-IV-TR Diagnostic Criteria for Opioid Withdrawal.

A. Either of the following:
    a. Cessation of (or reduction in) opioid use that has been heavy and prolonged (several weeks or longer).
    b. Administration of an opioid antagonist after a period of opioid use.
B. Three (or more) of the following, developing within minutes to several days after Criterion A:
    a. Dysphoric mood
    b. Nausea or vomiting
    c. Muscle aches
    d. Lacrimation or rhinorrhea
    e. Pupillary dilation, piloerection, or sweating
    f. Diarrhea
    g. Yawning
    h. Fever
    i. Insomnia
C. The symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D. The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder (8).

Autonomic arousal may also occur during withdrawal.

4. It is possible that some patients might abuse ULTRACET to self-medicate a psychiatric disorder. Case reports suggest that tramadol may precipitate mania or worsen depression (9). Tramadol inhibits the reuptake of norepinephrine and serotonin. Therefore, psychiatric patients (especially patients with a history of depression or mania) might need to be more closely monitored while taking ULTRACET. A depressed patient might be tempted to increase the dose if

ULTRACET causes the patient to feel better. In addition, some patients with a history of mania enjoy feeling manic (because they may accomplish a great deal if their thoughts are not disorganized) and perhaps might increase the dose if they experience euphoria due to tramadol.

5. Raphael J. Leo *et al.* state that a contract which addresses the following may be useful if a patient with a history of substance abuse requires tramadol:
   (a) The frequency that tramadol will be prescribed;
   (b) How "lost" and "stolen" prescriptions will be handled; and
   (c) If... another source is sought... to prescribe more tramadol than originally prescribed, the PMD (primary medical doctor) should be contacted directly (10).

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References

1. PDR Electronic Libarary. PDR entry for Ultram Tablets, p 7,8.

2. See #1, p 14.

3. Villamanan JCR, Blanco CA, Sanchez AS, Carvajal A, Arias LM, Garcia del Pozo J (May 2000), Letters – Withdrawal syndrome after long-term treatment with tramadol. The RCGP-British Journal of General Practice.

4. Leo RJ, Narendran R, DeGuiseppe B (2000), Brief report-Methadone detoxification of tramadol dependence. J Substance Abuse Treatment 19, p 298.

5. Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Goodman Gilman A, eds. (1996), Goodman and Gilman's The Pharmacological Basis of Therapeutics, 9th ed, p 533.

6. Kesavan S, Sobala GM (September 1999), Serotonin syndrome with fluoxetine plus tramadol. J Royal Society Med 92, p 474.

7. See #6; Weiner LA, Smythe M, Cisek J (1998), Serotonin syndrome secondary to phenelzine-venlafaxine interaction. Pharmacotherapy 18, p 399-403.

8. DSM-IV-TR (STAREF). Entries for Opioid Intoxication and Opioid Withdrawal.

9. See #4, p 297.

10. See #4, p 299.

Y. Kong

M E M O R A N D U M

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

Date: August 30, 2000

To: Dr. Karen Midthun
Director, Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products (HFD-550)

From: Michael Klein, Ph.D. /S/
Office of the Center Director
Controlled Substance Staff (HFD-009)

Through: Dr. Deborah B. Leiderman /S/
Director, Controlled Substance Staff (HFD-009)

Subject: NDA # 21-123.
Tramadol hydrochloride (37.5 mg)/Acetaminophen (325 mg):
Abuse Liability Review
Sponsor: RWJohnson PRI

This memorandum is in response to the request of the Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products, to review the abuse liability assessment package of NDA # 21-123.

SUMMARY:

In 1999, the Abuse Liability Assessment Package of NDA # 21-123 for the combination product of tramadol and acetaminophen was submitted to the Division of Anesthetic, Critical Care and Addiction Drug Products (HFD-170) for review. Following a CDER reorganization in 2000, the review responsibility continued and was conducted by the Controlled Substance Staff (CSS) in the Office of the Center Director (HFD-009).

Information provided in the Abuse Liability Assessment Package of NDA #21-123 was largely material that had been previously reviewed and addressed by the Drug Abuse Advisory Committee (in 1994 and 1998). The abuse-related data that was submitted concerned abuse of the single entity product (**Ultram®**) (NDA # 20-281); this data was cross-referenced for review and consideration of NDA # 21-123. Although compelling, this information did not specifically relate to the new drug product, but primarily to the drug substance, tramadol.

The reviewable material included adverse event data (also reviewed by OPDRA), the final report of RW Johnson PRI's *Independent Steering Committee* (the data of which was included in the OPDRA review), published scientific literature on the pharmacology

of tramadol, and the Phase 4 final study report of surveillance of participants in impaired health professionals to determine the incidence of abuse of tramadol **(Ultram®)**. Also, CSS has supplemented the data with an update of data from the Drug Abuse Warning Network (DAWN).

Subsequent to HFD-550's approvable action on the product, the medical officer review of NDA # 21-123 became available for review by CSS. From the clinical review, CSS became aware of considerable data related to abuse and dependence for the drug product; this information was not part of the Abuse Liability Assessment Package of the NDA. Also available is the summary of reports of iatrogenic dependence from the medical review of the osteroarthritis trial for **Ultram®**, which was also made available by HFD-550.

ADVERSE DRUG EVENTS RELATED TO ABUSE & DEPENDENCE.

Tramadol **(Ultram®)** was approved by FDA in March 1995. Between April 1995 and November 1998, an estimated [redacted] individuals were exposed to tramadol. During that period, the sponsor received a total of 3,462 U.S. post-marketing adverse event reports, including 120 deaths. Thirty-one percent were classified as serious.

Updated listings of adverse events provided to HFD-550 in August 1999 contained a total of 205 deaths from all sources. These included 17 patient reports identifying cases termed psychiatric (suicide N=9; drug abuse N=5; drug dependence N=1; and delirium N=2). The sponsor estimated that 43 deaths were associated with overdose of tramadol. Total reports of overdose at that time involved 332 cases. **Table 1** (below) updates adverse event reports for Ultram that are related to abuse to January 31, 2000.

TABLE 1. Tramadol Cumulative Adverse Event Reports 03/03/95 – 01/31/00.

Preferred Term (Age)	U.S. Reports	Other Reports	Total
Drug Abuse	317	9	326
Drug Dependence	229	10	239
Increased Tolerance	12	0	12
Withdrawal Syndrome	447	33	480
Therapeutic Response Increased (Age≤ 6)	8	14	22
Therapeutic Response Increased Intentional (Age> 6)	127	28	155
Therapeutic Response Increased Accidental (Age> 6)	8	2	10
Therapeutic Response Incr.Undeter. Intent (Age> 6)	208	21	228
Number of Patients with Any of Above*	1007	101	1108

Withdrawal syndrome included signs and symptoms of physical dependence such as irritability, nervousness, headache, abdominal cramps, chills, difficulty sleeping. Approximately 40% of the cases involved a high dose (>400 mg/day) or prolonged use (>6 months).

Therapeutic Response Increased Intentional n=12, and *Therapeutic Response Increased Undetermined Intent* n=18, *Number of Patients TOTAL* n=141.

*Each case may be listed under more than one preferred term. Therefore, column total (1353 for U.S., 1473 worldwide) exceeds the number of people with any of the listed conditions (1007 for the US, 1108 worldwide).

PHASE 4 FINAL STUDY REPORT OF IMPAIRED HEALTH PROFESSIONALS.

The Phase 4 final study report of surveillance of participants in impaired health professional programs in four states was submitted to determine the incidence of abuse of tramadol (**Ultram®**). Impaired health care professionals (N = 1,601) who were active participants in the monitoring programs were recruited for the study. The protocol was designed to follow each participant's use of tramadol (**Ultram®**) and persistent non-medically sanctioned use. Urine samples of participants were tested by the Sponsor.

One hundred forty (140; 8.74%) of the impaired health care professionals in the study had at least one urine sample that was positive for tramadol. Eighty-seven of the 140 subjects (62.1%) did not have a legitimate prescription and practiced some level of experimentation. Twenty-six subjects (1.6% of total sample; 15% of tramadol-exposed population) met study criteria that was defined as "extensive experimentation". Most of these tramadol users had previous histories of opioid abuse.

Fifteen participants (0.94% of total; 10.7% of tramadol users) found tramadol to be superior to other drugs they had abused or they felt that it was a drug that could easily avoid detection because it was not scheduled in the CSA.

CASES OF ULTRAM® DEPENDENCE FROM OA CLINICAL TRIAL.

Supplemental NDA (#20-281, S018) was intended to provide evidence of efficacy and safety of Ultram® in management of signs and symptoms of osteoarthritis (OA), but failed, and resulted in reports of cases of tramadol dependence.

Patients presented with withdrawal symptoms after Ultram® discontinuation. Symptoms appeared between 1 and 5 days after discontinuation and lasted between 4 and 7 days. Four of the patients had received Ultram® (200-400 mg/day) for more than 6 months, as part of the open-label extension of one study. Of the 38 patients that received Ultram® for more than 6 months, the incidence of withdrawal at this exposure time was 10.5%. Symptoms included restlessness, insomnia, muscle twitching, decreased appetite, nausea, chills, sweats, depression, visual hallucinations, agitation, dyspnea, nervousness, abdominal pain. Two other patients that had received Ultram® for 2-1/2 months in another study were reported to have also become dependent on the drug.

DRUG ABUSE WARNING NETWORK (DAWN).

Table 2 (below) shows Drug Abuse Warning Network (DAWN) data, i.e., the estimated number of mentions for tramadol and similar drugs by year. The most common reason for emergency department (ED) mentions related to acetaminophen/codeine products and tramadol was overdose.

TABLE 2. Number of estimated emergency department (ED) drug mentions of tramadol and other drugs, by year for 1995-1998. Number of estimated ED mentions expressed as percentage of the total number of drug mentions for each drug annually, in parenthesis ( ).

DRUGS	TOTAL MENTIONS			
	1995	1996	1997	1998
TRAMADOL (ULTRAM)	645 (0.1%)	1,290 (0.25%)	1,418 (0.27)	1,973 (0.4%)
DEXTRO-PROPOXYPHENE	7,015 (1.4%)	6,779 (1.3%)	7,614 (1.4%)	6,883 (1.3%)
ACETAMINOPHEN/ CODEINE	6,829 (1.3%)	5,833 (1%)	6,589 (1.3%)	5,044 (1%)
HYDROCODONE	8,977 (1.7%)	10,474 (2%)	10,706 (2%)	12,570 (2%)
TOTAL EPISODES	513,633	514,347	527,058	542,544

In 1998, there were 36 of ten thousand ED episodes for tramadol as compared to 92 per ten thousand episodes for codeine/acetaminophen, 126 per ten thousand episodes for dextro-propoxyphene, and 231 of ten thousand episodes for hydrocodone.

Single use of tramadol accounted for 12%, 35%, 18% and 26% of total mentions for 1995, 1996, 1997 and 1998, respectively. Other drugs mentioned in combination with tramadol were alcohol, cyclobenzaprine, clonazepam, hydrocodone and alprazolam.

Table 3 (below) contains data from the National Prescription Audit Plus, IMS Health and are projected total number of prescriptions (new and refill) dispensed by U.S. retail pharmacies (chain, independent and food stores) including mail orders.

TABLE 3. Drug Utilization Values Reported as Annual Prescription Sales in the U.S.A. (In Thousands) For Ultram®/Tramadol, Dextro-Propoxyphene, Acetaminophen/Codeine, and Hydrocodone (1995-1998).

DRUGS	PROJECTED TOTAL PRESCRIPTIONS [a]			
	1995	1996	1997	1998
ULTRAM/TRAMADOL				
DEXTRO-PROPOXYPHENE [b]				
ACETAMINOPHEN/ CODEINE [b]				
HYDROCODONE [b]				

[a] Source: IMS America NPA + TCR, On-line. Not for use outside FDA without prior clearance by IMS America. [b] Controlled Substance

The frequency of ED mentions relative to total number of prescriptions for 1998 for Ultram ®/ tramadol is approximately 1.9 per ten thousand prescriptions. For the same period of time, the frequency of ED mentions per ten thousand prescriptions is approximately 2.1 for acetaminophen/codeine products, 1.8 for hydrocodone, and 2.3 for dextro-propoxyphene. Frequency of reporting for tramadol is comparable to those of acetaminophen/codeine, hydrocodone and dextro-propoxyphene products.

SUMMARY OF DRUG ABUSE & DEPENDENCE DATA FROM THE MEDICAL OFFICER REVIEW OF NDA #21-123 Tramadol/APAP

Clinical development to evaluate efficacy and safety of the Tramadol/APAP in the management of moderate to moderately severe pain included a total of 19 clinical studies listed below:

[redacted]

2. TRAMAP-ANAG-011: A single-dose trial in a dental pain model that had data integrity problems and was terminated early
3. Seven controlled, single-dose, double-blind trials in dental pain: TRAMAO-ANAG-002, 003, 010, 012, 013), including a dose-ranging trial (Protocol TRAMAP-ANAG-007) that was sponsored by [redacted] and an aborted trial (Protocol TRAMAP-ANAG-011).
4. Two controlled, single-dose, double-blind trials in surgical pain (Protocols TRAMAP-ANAG-004 and –005).
5. Two single-dose pilot studies in dental (Protocol CA) or surgical (Protocol CB) pain.

[redacted]

7. **Four clinical pharmacokinetic studies in healthy volunteers (Protocols TRAM-PHI-001, TRAMAP-PHI-001, TRAMAP-PHI-002, and TRAMAP-PHI-003).**

The drug development program was classified by two study types: Single-dose trials and Multiple-dose trials. The single-dose trials consisted of two different study models: dental pain and surgical pain. **As they are single-dose studies, it is very unlikely that abuse or dependence would be shown.** [redacted]

TABLE 4. Number of subjects participating in trials with tramadol/APAP.

Subject Population	Total Enrolled & Randomized	Total Randomized & Treated with TRAM/APAP
Subjects with acute or chronic pain	3,783[a]	1,302
Single-Dose Trials	2,775	634
Pivotal Dental Pain[b]	1,200	240
Supportive Dental Pain[c]	1,015	253
Supportive Surgical Pain[d]	560	141
Multiple-Dose Controlled Trials[e]	1,008	579
Long-term Exposure	396[f]	396[f]
Healthy Volunteers[g]	92	87
TOTAL SUBJECTS	3,875	1,389

[redacted] Thus, a total of 3,946 subjects with acute [redacted] pain were enrolled into one of the trials included in this ISE. [b] TRAMAP-ANAG-010, 012, and 013 [c] TRAMAP-ANAG-002, 003, 007 and CA [d] TRAMAP-ANAG-004, 005, and CB

[redacted]

[g] TRAM-PHI-001, TRAMAP-PHI-001, TRAMAP-PHI-002, TRAMAP-PHI-003. 3 of these studies (TRAMAP-PHI-001, -002, -003) were crossover in design; 5 subjects discontinued prematurely before receiving Tramadol/APAP.

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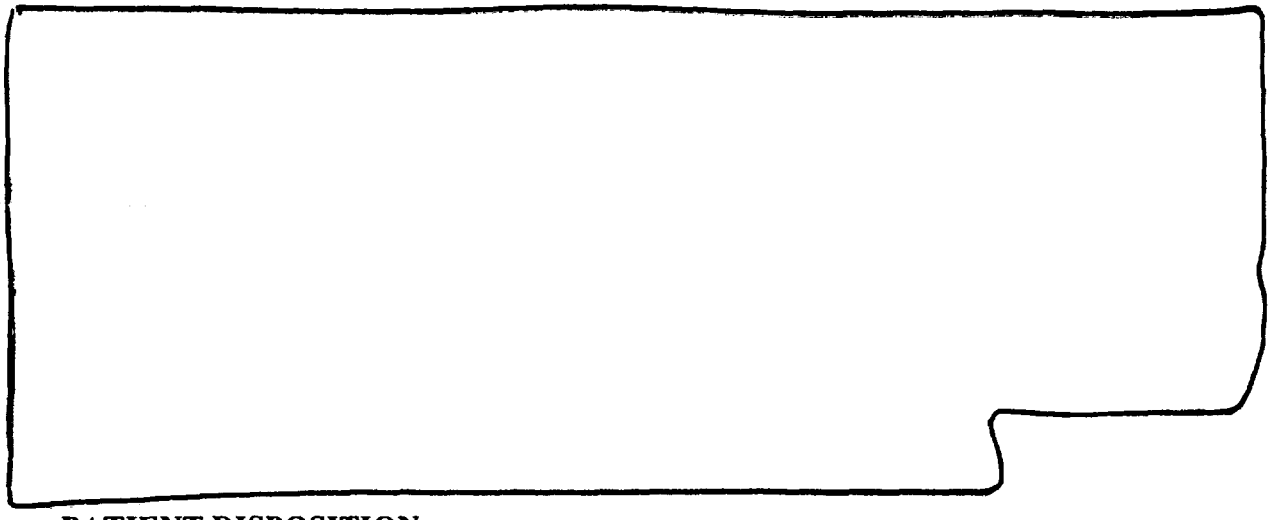


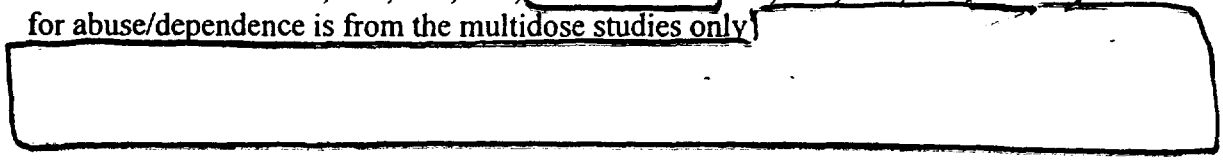
PATIENT DISPOSITION.

Across all 3 multiple dose trials, 990 randomized subjects were evaluable for efficacy. Of these, 791 (80%) completed the double-blind phase of their respective trial as planned and 199 (20%) discontinued double-blind therapy prematurely. Of the 199, 132 withdrew due to an adverse event, 33 left by choice, 11 were lost to follow-up, and 23 withdrew for other reasons. Withdrawals were comparable across all analgesic groups.

Efficacy results: Combination has similar analgesic effects when compared to the 2 active control arms (APAP/COD & IBU). However, there was no placebo in these studies.

SAFETY FINDINGS.

The primary source of safety data came from both single dose [redacted] studies: TRAMAP-ANAG-002, 003, 004, 005, [redacted] 010, 011, 012, 013, [redacted] Focus for abuse/dependence is from the multidose studies only



See Page 82 & 83 of review by Dr. Lee for evaluable patients.
See Page 85-6 for serious AE in multiple dose trials.
See Page 91, Patient 33007 who experienced withdrawal syndrome after being on drug for 183 days & then taken off.
See Page 92, Patient 18006 for Drug Abuse, Anxiety Attack. On day 36, subject could not continue in study because he was moving out-of-state. On Day 39, the subject returned medication bottles empty, although based on diary there should have been 160 tablets left.

ADVERSE EVENTS-discontinuation from studies.

There were 1,919 randomized subjects (1,909 of these subjects were evaluable for safety) exposed to Tramadol/APAP across the 12 primary clinical trials. Of the 1,919 subjects, 1,243 (65%) completed their respective trials and 676 (35%) discontinued treatment prematurely. Of the 676 exposed subjects who withdrew, 341 were due to an adverse event, 150 left by choice, 36 withdrew for lack of efficacy, 29 were lost to follow-up, and 120 withdrew for other reasons.

Adverse drug events that were reported by at least 3 subjects who withdrew due to an adverse event by preferred term for subjects exposed to Tramadol/APAP in the primary clinical trials were as follows. Most common reasons for discontinuation from treatment were nausea (107), dizziness (67), somnolence (42), vomiting (41), headache (37), pruritus (27) and constipation (25). Profiles of treatment-limiting adverse drug events identify TRAM/APAP-related side effects, and most of them were associated with tramadol.

Dropouts.
Across the four trials, 1,051 (73%) of the 1,437 Tramadol/APAP-exposed subjects had at least one adverse drug event. The most common adverse event occurred in the GI system, CNS, or were psychiatric disorders, and consisted of nausea (18%), dizziness (15%), somnolence (12%), constipation (11%), and headache (11%). CNS stimulation effect was 6%.

Psychiatric Disorders.
Anorexia, Anxiety, Confusion, Euphoria, Insomnia, Nervousness, Somnolence.

Drug Abuse Section.

See page 109-110 of the Medical Officer review. 6%:

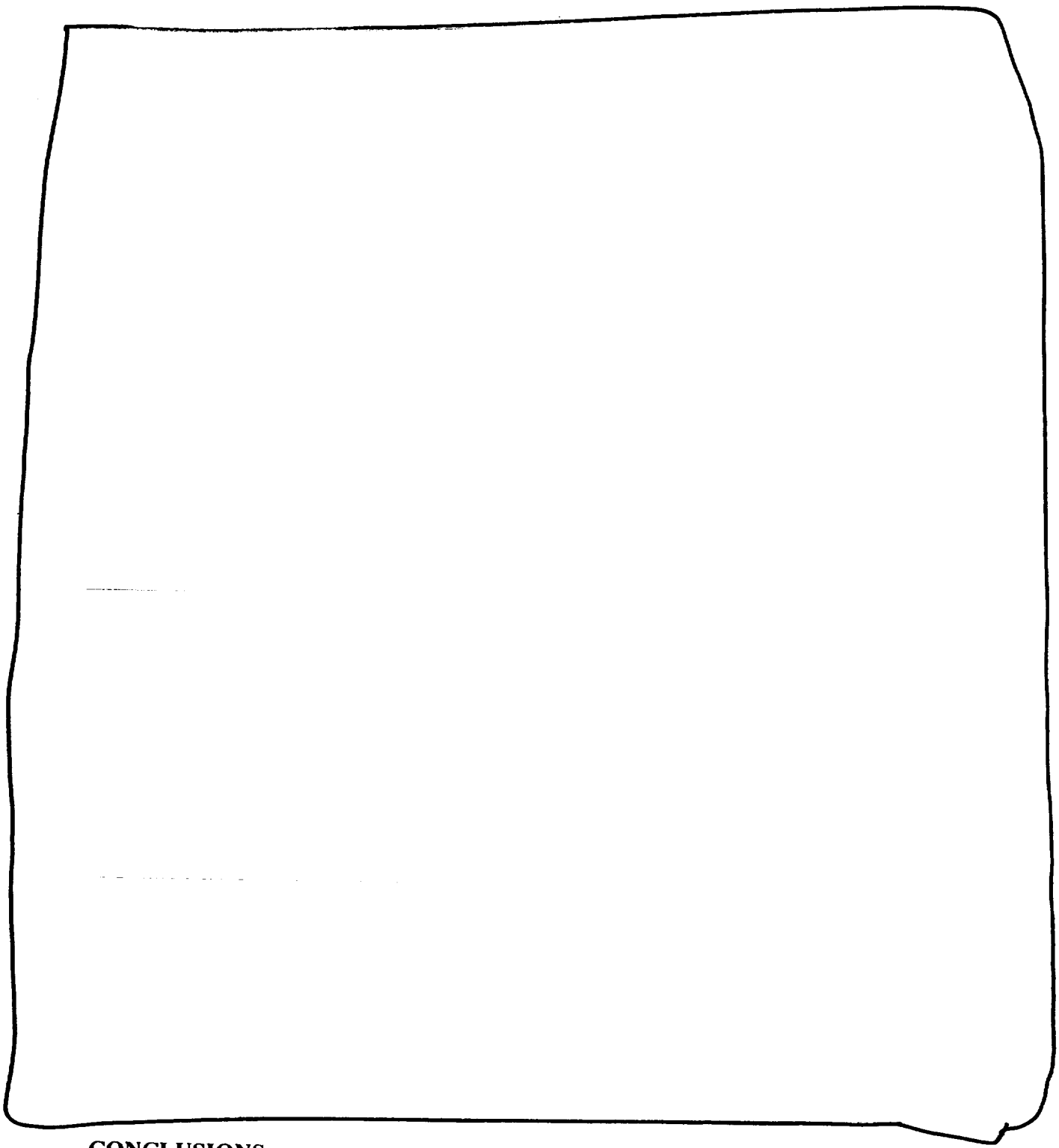
Treatment emergent adverse events related to dependence/abuse and withdrawal are summarized based on discussions between the Sponsor and FDA (February 1999). FDA requested that patients experiencing withdrawal, dependence, and abuse-related adverse event terms be evaluated. **Table 6** below presents these FDA terms and their mapping to the WHOART adverse event dictionary used in the ISS database.

TABLE 6. TERMS RELATED TO DEPENDENCE/ABUSE & WITHDRAWAL.

FDA Coded Term	ISS Coded Term	Constellation No.[a]
Craving (drug-seeking behavior, possible overdose & tolerance development)	Drug abuse, (drug) dependence, tolerance increase, withdrawal syndrome, therapeutic response increased (overdose)	6
Nausea or Vomiting	Nausea, vomiting	5
Pain (muscle aches, headache, back pain, rigors, etc.	Myalgia, headache, back pain, rigors, abdominal pain	4, 5, 1
Lacrimation or rhinorrhea	Lacrimation abnormal, rhinitis	4
Pupillary dilation, piloerection, or sweating	Vasodilation, piloerection, sweating increased	1
Diarrhea	Diarrhea	5
Fatigue (yawning)	Fatigue, yawning	2, 6
Fever	Fever	1
Insomnia (sleep disorders)	Insomnia	2
Anxiety, nervousness	Anxiety, nervousness	3
Depression (dysphoria)	Depression	6
Irritability	Nervousness	3
Respiratory difficulties	Dyspnea	1
Hallucinations	Hallucination	6
Suicide attempts	Suicide attempt	6

[a] For summaries using constellations of coded terms, see text that follows this Table.
Data Source: Based on the Sponsor's Table in the Drug Abuse & Overdose Information.

To be counted in the above Table 6 performed for the Tramadol/APAP-exposed subjects of the 4 long-term pain trials, subjects were to have had one or more coded terms within at least 3 of the 6 categories of terms. Subjects are also counted in the summary if they had one or more coded terms within at least 2 of the 6 categories of terms occurring within one week of drug discontinuation. Taken together, the results of the clinical trials suggest that incidence of dependence/abuse and withdrawal may be up to 6% of the study population.



CONCLUSIONS.

The results of the long-term multiple dose clinical trials suggest that incidence of dependence/abuse and withdrawal may be as high as 6% of the study population. This is not a drug abusing population. In addition, there is a large number of patients who

experienced "influenza-like symptoms". Preclinical and clinical data show that tramadol produces μ-opioid activity comparable to other opioids.

Ultram® has a similar adverse events profile as other opioids, including CNS depression, drug abuse, drug dependence and withdrawal.

From the impaired health care professionals and osteoarthritis studies, denominator data has been provided to be able to calculate the percent of subjects who become dependent or abuse the drug relative to the total number exposed to the drug (approximately 10%).

Reports of abuse and dependence in MedWatch continue, but is not at an increasing rate.

DAWN shows annual increases in estimated ED mentions for tramadol for each year from 1995 to 1998. The annual percentages of drug episodes relative to total number of episodes of all drugs in the DAWN system are increasing for tramadol, but not for the comparator drugs. The number of ED mentions for tramadol relative to all ED mentions is of the same order of magnitude as those of dextro-propoxyphene, and tenfold less than those of codeine and hydrocodone preparations.

Original NDA 21-123
HFD-009/LeidermanD
HFD-009/MoodyC
HFD-009/KleinM
HFD-009/Calderons
HFD-550/MidthunK
HFD-550/KongY
HFD-550/VillalbaM
HFD-550/VacarriL
HFD-550/GoldkindL

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