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

Sincerely,
The R.W. Johnson
Pharmaceutical Research Institute

Natasha Rogozenski

Natasha Rogozenski
Assistant Director
Regulatory Affairs

cc: Dr. Yoon Kong (HFD-550) (**2 DESK COPIES**)

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

NDA ORIG AMENDMENT

APR - 3 2000

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

NDA 21-123
ULTRACET™
37.5 mg Tramadol hydrochloride/
325 mg acetaminophen combination tablets

AMENDMENT TO PENDING NDA
Printing Error Correction -
Response to Biopharmaceutics Reviewer Comments Dated 10 March 2000

BB

Dear Sir/Madam:

Reference is made to NDA 21-123 submitted 31 August 1999 for the combination product, ULTRACET ™37.5 mg tramadol hydrochloride/325 mg acetaminophen tablets. Reference is also made to a fax from the Agency dated 10 March 2000, wherein the Biopharmaceutics Reviewer presented several questions related to the pending NDA and requested a response by 17 March 2000. Finally, Reference is made to our subsequent response, dated 17 March.

It has come to our attention that there may be a printing error on some copies of two of the figures presented in our 17 March response. In some copies, Figures B2 and B3 located in Tab B4 (pages identified as 56 and 57 in the last two digits of the footer), did not print all of the black curved lines for APAP. Although the Agency's copies may not be affected, to ensure that the Agency has correct pages in all copies, we are providing four copies of those pages as replacement pages. One copy is for the archives, one copy for Dr. Yoon Kong, Project Manager, and two desk copies, as previously provided to Dr. Kong.

ORIGINAL

ologize for any inconvenience this replacement may cause. Should you have any ...s please contact me directly at (908) 704-4222 or our phone number dedicated for FDA use at (908) 704-4600.

Sincerely,

Natasha Rogozenski

Natasha Rogozenski
Assistant Director
Regulatory Affairs

cc: Dr. Yoon Kong (HFD-550) (**2 DESK COPIES**)

BB 3-30-1 FAX

3-29-00

\\RARUSRARES01\PRIUSREG\ULTRAM\ULTRACET\NDA responses to FDA comments\Amend to 17 March Biopharm Ques - Printing Error.doc

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

APR - 7 2000

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

NDA 21-123 - ULTRACET™
37.5 mg Tramadol hydrochloride/
325 mg acetaminophen combination tablets

GENERAL CORRESPONDENCE
Response to Chemistry, Manufacturing and Controls Questions of March 28, 2000

Dear Sir/Madam:

Reference is made to NDA 21-123 submitted 31 August 1999 for the new combination product ULTRACET™, 37.5 mg tramadol hydrochloride/325 mg acetaminophen tablets. Reference is also made to a facsimile dated 28 March 2000 from the Agency containing comments regarding Chemistry, Manufacturing and Controls information in NDA 21-123. Reference is also made to a telephone message from Dr. Yoon Kong on 06 April 2000 where FDA requested that we submit our specific comments and questions for further discussion prior to scheduling a telephone conference.

At this time, The R.W. Johnson Pharmaceutical Research Institute (RWJPRI) is submitting, in duplicate, our specific questions, comments and draft responses to the Chemistry Reviewer's comments contained in the Agency's fax of 28 March 2000. We respectfully request to schedule a telephone conference to discuss these issues further.

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

Sincerely,

Natasha Rogozenski

Natasha Rogozenski
Assistant Director
Regulatory Affairs

ORIGINAL

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

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

NDA [illegible]

BB

APR 1 3 2000

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

NDA 21-123
ULTRACET™
37.5 mg Tramadol hydrochloride/
325 mg acetaminophen combination tablets

AMENDMENT TO PENDING NDA
Response to Biopharmaceutics Reviewer
Request Dated 10 April 2000

Dear Sir/Madam:

Reference is made to NDA 21-123 submitted 31 August 1999 for the combination product, ULTRACET ™37.5 mg tramadol hydrochloride/325 mg acetaminophen tablets. Reference is also made to a telephone voice mail message from Dr. Yoon Kong, [illegible]ct Manager, to Ms. Natasha Rogozenski on 10 April 2000, wherein she presented the following request from the Biopharmaceutics reviewer regarding the pending NDA 21-123, and more specifically, our 17 March 2000 submission of Population PK/PD analysis: "Provide PK data for the M1 metabolite in Excel format for the six clinical trials that were pooled for PK/PD analysis."

At this time, The R.W. Johnson Pharmaceutical Research Institute (RWJPRI) is submitting a response to the question presented in the 10 April request from the Biopharmaceutics reviewer. Four copies of a diskette containing the data in Excel format are provided. One copy is provided for each of the following: FDA Archives; FDA Electronic Document Management; DESK COPY for Dr. Yoon Kong, Project Manager, and DESK COPY for Dr. Kong to forward to the Biopharmaceutics Reviewer.

ORIGINAL

N:\ULTRAM\ULTRACET\NDA responses to FDA comments\Response to Biopharm Reviewer Request 10 April Cov Ltr.doc

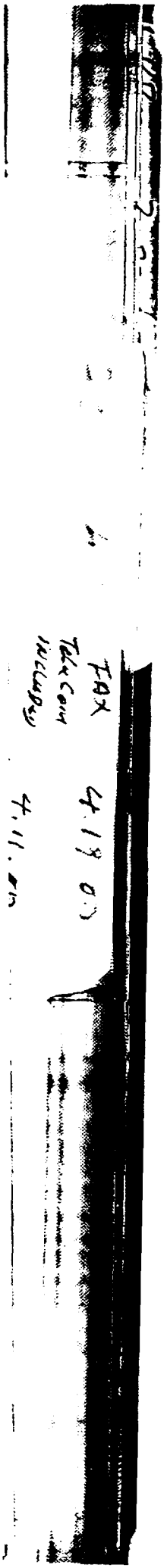
Should you have any questions please contact me directly at (908) 704-4222 or our e number dedicated for FDA use at (908) 704-4600.

Sincerely,

Natasha Rogozenski

Natasha Rogozenski
Assistant Director
Regulatory Affairs

cc: Dr. Yoon Kong (HFD-550) **(2 DESK COPIES)**



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

APR 2 0 2000

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

NDA 21-123
ULTRACET™
37.5 mg Tramadol hydrochloride/
325 mg acetaminophen combination tablets

AMENDMENT TO PENDING NDA
Response to Biopharmaceutics Reviewer
Request Dated 19 April 2000

EB

Dear Sir/Madam:

Reference is made to NDA 21-123 submitted 31 August 1999 for the combination product, ULTRACET™ 37.5 mg tramadol hydrochloride/325 mg acetaminophen tablets. Reference is also made to a fax from Dr. Yoon Kong, Project Manager dated 18 April 2000, wherein she presented the following request from the Biopharmaceutics reviewer regarding the pending NDA 21-123:

> "The PK/PD analysis was performed using tramadol pharmacokinetics data from patients in one of the ULTRAM clinical trials. It appears that the coadministration of acetaminophen affects the pharmacokinetics of tramadol. Please provide justification why that data was preferred over the tramadol pharmacokinetics data from phase I trials for Ultracet."

The biopharmaceutics reviewer requested a response by 27 April to facilitate the review progress. At this time, The R.W. Johnson Pharmaceutical Research Institute (RWJPRI) is submitting the attached response to the question presented in the 19 April request.

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

Sincerely,

Natasha Rogozenski

Natasha Rogozenski
Assistant Director
Regulatory Affairs

ORIGINAL

cc: Dr. Yoon Kong (HFD-550)

N:\ULTRAM\ULTRACET\NDA responses to FDA comments\Response to Biopharm Reviewer Request 19 April Cov Ltr.doc

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

APR 2 8 2000

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

NEW CORRESPONDENCE

IND 50,138
ULTRACET™
37.5 mg Tramadol hydrochloride/
325 mg acetaminophen combination tablets

Serial No.: 0 9 6

NC

Cross Refer to:
NDA 21-123 ULTRACET™

IND [redacted] ULTRAM®
(tramadol HCl tablets)

Serial No.: 2 7 3

CORRESPONDENCE
Diabetic Neuropathy
Program Proposal and Teleconference Request

Dear Sir/Madam:

Reference is made to IND [redacted] for tramadol/acetaminophen combination product, filed on 15 March 1996, and to NDA 21-123 submitted 31 August 1999 for the combination product, ULTRACET™ (37.5 mg tramadol hydrochloride/325 mg acetaminophen tablets), currently under Agency review. Reference is also made to IND [redacted] for ULTRAM (tramadol hydrochloride tablets). Additionally, reference is made to teleconferences with the Agency on December 2, 1999 and January 6, 2000 to discuss possible developmental programs, including a program for neuropathic pain. Sponsor participants included representatives from The R.W. Johnson Pharmaceutical Research Institute (RWJPRI) and [redacted]

Please refer to the Background Overview of Regulatory Correspondence with the Agency on this topic contained in Attachment 1. We thank the Agency for their 6 January 2000 teleconference minutes, which are also provided in Attachment 1. Please note, however, that the Background Information provided in the Agency's minutes refers to IND [redacted] There are no supplements with those numbers.

DUPLICATE

BB 4-20-1 For 4.26.00 R.T.C 2.28.00

At this time, we wish to follow-up on the 6 January 2000 meeting and provide the Agency with a proposal for our Target Development Program in support of the new indication for ULTRACET™ in the treatment of painful diabetic neuropathy which follows. We propose to study ULTRACET™, a combination analgesic, as a treatment for the pain of diabetic neuropathy utilizing two types of clinical trials.

In a six-week double blind placebo controlled study (Protocol TPS DN, final report submitted to IND [redacted] on 28 December 1998, Serial No. 239) we demonstrated that tramadol is effective for the treatment of the pain of diabetic neuropathy. Animal studies of pain indicate that the combination analgesic ULTRACET™ (37.5mg tramadol and new 325mg acetaminophen) is synergistic, supportive of anecdotal reports from clinicians who indicate that the addition of acetaminophen to tramadol enhances the analgesic effect of tramadol in patients.

The first study was designed to fulfil the requirements, per *the Guidance for Industry: Guideline for the Clinical Evaluation of Analgesic Drugs*, Revised December 1992, to utilize a factorial design for studying combinations of analgesics to demonstrate that the combination produces more beneficial effects than either drug alone. Therefore, the first trial will be a two-week, four-arm study comparing fixed doses of ULTRACET™ three times daily to tramadol, acetaminophen and placebo in a factorial design. [redacted]

We believe a two-week factorial study should be adequate to prove the hypothesis that the combination is truly superior to each of its components. This is consistent with current guidelines (*Guideline for Clinical Evaluation of Analgesic Drugs, Revised December 1992*) that merely require a single dose study to prove that a combination product meets the combination rule and yet allows for prolonged use of the drug if other studies of durability of effect and safety are met. We are prepared to replicate this study. A synopsis is provided as Attachment 2.

In addition, to fulfil the requirement for durability of effect, we are also proposing to conduct an additional three-month study of the combination product versus placebo using a prn-dosing regimen. A synopsis of this study is provided as Attachment 3.

We would like to schedule a teleconference with the Agency to discuss our proposals for a diabetic neuropathy program and indication. The question posed to the Agency for discussion during our requested teleconference follows:

> If the proposed studies are successful, we believe this will provide adequate evidence for the safety and efficacy of ULTRACET™ in the treatment of painful diabetic neuropathy. Given the plan outlined herein, and assuming that these studies are successful, would this be acceptable to the Agency to support this labeling indication ?

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

Sincerely,

Peggy Ferrone

for Natasha Rogozenski
Assistant Director
Regulatory Affairs

cc: Dr. Yoon Kong (HFD-550)

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

MAY - 1 2000

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

NDA 21-123 - ULTRACET™
37.5 mg Tramadol hydrochloride/
325 mg acetaminophen combination tablets

GENERAL CORRESPONDENCE
Final Response to Chemistry,
Manufacturing and Controls Questions of
28 March 2000

AMENDMENT
BC

Dear Sir/Madam:

Reference is made to NDA 21-123 submitted 31 August 1999 for the new combination product ULTRACET™, 37.5 mg tramadol hydrochloride/325 mg acetaminophen tablets. Reference is also made to a facsimile dated 28 March 2000 from the Agency containing comments regarding Chemistry, Manufacturing and Controls (CMC) information in NDA 21-123 and to a teleconference regarding these CMC comments that took place on 11 April 2000 with The R.W. Johnson Pharmaceutical Research Institute (RWJPRI) and the Agency. In addition, we refer to FDA minutes of the 11 April 2000 teleconference received by facsimile transmission on April 19, 2000.

At this time, RWJPRI is submitting, in duplicate, our final responses to the Chemistry Reviewer's comments contained in the Agency's fax of 28 March 2000, as well as a response to an additional FDA question regarding the storage statement for drug product that was raised during the 11 April 2000 teleconference. We have also included final artwork for the proposed component packaging labels that contain the revised storage statement for your review.

We have reviewed the Agency's minutes from the 11 April 2000 teleconference and would like to note a discrepancy regarding action item no. 1 which states, "The sponsor will provide moisture content values for current batch of drug product and future batches in stability specification of CMC." Our viewpoint differs with respect to the agreement made during the 11 April 2000 teleconference regarding the Agency's suggestion to include a moisture content specification for initial release and stability. During the teleconference, we indicated that moisture testing has not been part of the stability program, and that we did not have data to set a moisture specification. We agreed to perform moisture testing on our current stability batches to determine if moisture is a concern, and to submit these data for the Agency's further consideration of this issue. Per our understanding of the agreements made

ORIGINAL

ATTACHMENT 1
MOISTURE TEST RESULTS

ATTACHMENT 2
NDA DRUG PRODUCT
SPECIFICATIONS

ATTACHMENT 3
DISSOLUTION DATA

FINAL ARTWORK:
PACKAGE COMPONENTS

BLISTER CARD

during the teleconference, this submission contains moisture data obtained during production of the four primary stability batches. Samples of all stability batches have been tested for moisture content, and all data have been provided for review. The results of the moisture testing indicate that moisture pickup is not a concern.

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

Sincerely,

Natasha Rogozenski

Natasha Rogozenski
Assistant Director
Regulatory Affairs

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

ATTACHMENT 1
MOISTURE TEST RESULTS

ATTACHMENT 2
NDA DRUG PRODUCT
SPECIFICATIONS

ATTACHMENT 3
DISSOLUTION DATA

ATTACHMENT 4
FINAL ARTWORK:
PACKAGE COMPONENTS

PHYSICIAN SAMPLE
BLISTER CARD

NDA ORIG AMENDMENT

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

MAY - 3 2000

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

NDA 21-123
ULTRACET™
37.5 mg Tramadol hydrochloride/
325 mg acetaminophen combination tablets

AMENDMENT TO PENDING NDA
Response to Biopharmaceutics Reviewer
Request Dated 26 April 2000

EE

Dear Sir/Madam:

Reference is made to NDA 21-123 submitted 31 August 1999 for the combination product, ULTRACET™ 37.5 mg tramadol hydrochloride/325 mg acetaminophen tablets. Reference is also made to a fax from Dr. Yoon Kong, Project Manager dated 26 April 2000, wherein she presented the following request from the Biopharmaceutics reviewer regarding the pending NDA 21-123:

> "In the population PK analysis, 2 subjects were considered CYP2D6 poor metabolizers. What are the criteria for designating an individual as a poor metabolizer (based on which PK parameters and what M1/parent ratio)? Also, the label refers to a drug interaction between acetaminophen and diflunisal, however, reference for this information cannot be located in the biopharmaceutics section of this NDA submission. Where can it be found in this NDA submission?"

The biopharmaceutics reviewer requested a response by 03 May to facilitate the review progress. At this time, The R.W. Johnson Pharmaceutical Research Institute (RWJPRI) is submitting the attached response to the questions presented in the 26 April request.

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

Sincerely,

Natasha Rogozenski

Natasha Rogozenski
Assistant Director
Regulatory Affairs

ORIGINAL

cc: Dr. Yoon Kong (HFD-550)

RESPONSE TO BIOPHARMACEUTICS REVIEWER REQUEST DATED 26 APRIL 2000

1. **FDA BIOPHARMACEUTICS REVIEWER REQUEST #1:**
"In the population PK analysis, 2 subjects were considered CYP2D6 poor metabolizers. What are the criteria for designating an individual as a poor metabolizer (based on which PK parameters and what M1/parent ratio)?"

RWJPRI Response:
The two subjects (1106 and 1109) in the TRAM-PHI-001 study were considered as CYP2D6 poor metabolizers based on the AUC(0-∞) Ratio of (+)-M1/(+)-Tramadol since CYP2D6 genotyping was not available in this study. CYP2D6 genotyping was available for subjects in three other Phase I studies (TRAMAP-PHI-001, TRAMAP-PHI-002 and TRAMAP-PHI-003). There is a very good correlation between AUC Ratios of (+)-M1/(+)-Tramadol and CYP2D6 genotyping results as shown in Table 1 on the following page. It is reasonable to consider subjects 1106 and 1109 as CYP2D6 poor metabolizers since their AUC ratios are much lower than the average ratio of all poor metabolizers.

APPEARS THIS WAY
ON ORIGINAL

RESPONSE TO BIOPHARMACEUTICS REVIEWER REQUEST DATED 26 APRIL 2000

Table 1: The AUC Ratio of (+)-M1/(+)-Tramadol in eight CYP2D6 poor metabolizers and seventy five normal metabolizers in four Phase I studies of Ultracet

Poor CYP2D6		Normal		Normal	
Subject ID[A]	Ratio of (+)-M1/ (+)-Tramadol	Subject ID	Ratio of (+)-M1/ (+)-Tramadol	Subject ID	Ratio of (+)-M1/ (+)-Tramadol
1106	0.00	1101	0.40	3201	0.13
1109	0.01	1102	0.13	3202	0.15
2101	0.00	1103	0.13	3203	0.17
2105	0.08	1104	0.36	3204	0.24
2106	0.15	1105	0.39	3205	0.26
3108	0.08	1107	0.57	3206	0.35
4104	0.00	1108	0.35	3207	0.15
4212	0.10	1110	0.18	3301	0.24
N	**8**	1111	0.28	3302	0.18
Mean	**0.05**	1112	0.37	3303	0.11
Min	**0.00**	2102	0.23	3304	0.11
Max	**0.15**	2103	0.42	3305	0.22
		2104	0.49	3306	0.36
		2107	0.42	3307	0.26
		2108	0.45	3308	0.29
		2109	0.38	3401	0.39
		2110	0.34	3404	0.29
		2111	0.57	3405	0.24
		2201	0.29	3407	0.13
		2202	0.13	4101	0.53
		2203	0.44	4102	0.16
		2204	0.44	4103	0.40
		2205	0.42	4105	0.28
		2206	0.37	4106	0.47
		2207	0.39	4107	0.31
		2208	0.54	4108	0.18
		2211	0.35	4109	0.29
		2212	0.24	4110	0.37
		3101	0.39	4111	1.20
		3102	0.28	4112	0.37
		3103	0.20	4201	0.43
		3104	0.16	4202	0.34
		3105	0.21	4203	0.47
		3106	0.32	4204	0.22
		(continued next column)		4205	0.29
				4206	0.49
				4207	0.59
				4208	0.42
				4209	0.54
				4210	0.44
				4211	0.51
				N	75
				Mean	**0.34**
				Min	**0.11**
				Max	**1.20**

[A] The first number of the subject ID indicates the study number;
Study 1= TRAM-PHI-001, Study 2=TRAMAP-PHI-002,
Study 3= TRAMAP-PHI-001, Study 4= TRAMAP-PHI-003

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

BM

MAY 16 2000

MAY 12 2000

MAY 16 2000

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
12229 Wilkins Avenue
Rockville, MD 20852

NDA 21-123
ULTRACET™
37.5 mg tramadol hydrochloride/
325 mg acetaminophen combination
tablets

AMENDMENT TO PENDING NDA
Correction to Two Files Contained in
CD-ROM #3 of 3 (Submitted on
13 September 1999)

NDA [illegible] AMENDMENT

Dear Sir or Madam:

Reference is made to NDA 21-123 submitted 31 August 1999 for the new combination product, ULTRACET™ (37.5 mg tramadol hydrochloride 325 mg acetaminophen) tablets and to the NDA Electronic Review Aid consisting of a three volume set of CD-ROMs submitted on 13 September 1999 as an Amendment supporting NDA 21-123. Additional desk copies were provided to Dr. Yoon Kong, Project Manager, on February 15, 2000. The current submission is with respect to CD-ROM #3 of 3.

It has come to our attention that CD-ROM #3 of 3 contained two errors. One dataset file was inadvertently omitted from the CD-ROM, and one file containing treatment assignments for a study was incorrect. At this time, we are providing the two files as follows:

ITEM 8 – CLINSTAT

- **Datasets\Protocols\Derived\Anag010\Advet010.xpt**
  File Advet010.xpt contains information on adverse events for the study TRAMAP-ANAG-010. This file was inadvertently omitted from the CD-ROM.
- **Datasets\Protocols\Raw\Anag002\Assign.xpt**
  File Assign.xpt is provided for the study TRAMAP-ANAG-002. This file contains *corrected treatment assignments* for the study. The enclosed file replaces the file of the same name, as previously provided.

Additionally, we have added the name of the file for the omitted "Advet010.xpt" listed above to the Electronic Index, which was provided on CD-ROM #1 of 3 in the 13 September submission.

ORIGINAL

Please note that the correct information for the first file being provided at this time: Datasets\Protocols\Derived\Anag010\Advet010.xpt was previously submitted in the original CD ROM to NDA 21-123 in file: Datasets\ISS\Group2\keyadve.xpt. Further, the correct information for the second file being provided at this time: Datasets\Protocols\Raw\Anag002\Assign.xpt was also provided (in its entirety) in several files provided in the original CD ROM #3 of 3 submitted to NDA 21-123. Specifically, the following files contain the information supplied in the aforementioned file:

- Datasets\Protocols Derived\Anag002\Ginft002.xpt;
- Datasets\Protocols Derived\Anag002\Proft002.xpt;
- Datasets\Protocols\Efficacy\Anag002\befft002.xpt;
- Datasets\Protocols\Efficacy\Anag002\lefft002.xpt; and
- Datasets\Protocols\Efficacy\Anag002\refft002.xpt.

Therefore, no new information to the application is being submitted at this time.

For ease of review, we are providing a complete revised set of all three of the CD-ROMs which were originally submitted on 13 September 1999. In accordance with recent discussions with Mr. Thomas Selnekovic and Mr. Barry Wheeler, FDA Office of Information Technology, with respect to electronic submissions, these CD ROMs do not contain ".doc" formats of any documents. Only ".pdf" and SAS versions are now provided.

In summary, one complete set of three CD-ROMs - ***Electronic Regulatory Submission for Archive*** is enclosed to be installed on the Agency's server with a note to the reviewers that a new file (Advet010.xpt) which was inadvertently omitted from the CD-ROM submitted on 13 September 1999 is being provided at this time; Assign.xpt has been corrected to agree with the hard copy of the original NDA submission; and the Electronic Index has been revised to include the new file, to delete the ".doc" and ".xls" formats of files and other minor corrections. (The .doc files have either been converted to pdf format, or duplicates in .doc format were removed). Therefore, please instruct the reviewers to disregard all mention of .doc (WORD 97) and .xls (MS Excel) files in the READ.ME and Electronic Reviewer's Guide, which have not been changed from the text provided in the original submission. These formats were provided in the 13 September 1999 submission, but have been omitted at this time, since, according to Guidelines, they cannot be installed on the FDA server. Two ***Reviewer Desk Copies*** are being provided directly to the Project Manager, Dr. Yoon Kong, HFD-550.

We wish to reiterate that the information contained in the two corrected files provided within this revised set of CD ROMs was provided correctly in other files contained on the original CD ROMs as well as in the hard copy of the NDA and does not change the results of the analysis supplied in the application. Only the Electronic Review Aid provided on CD-ROM is affected by this revision.

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

incerely,

he R.W. Johnson
harmaceutical Research Institute

Natasha Rogozenski

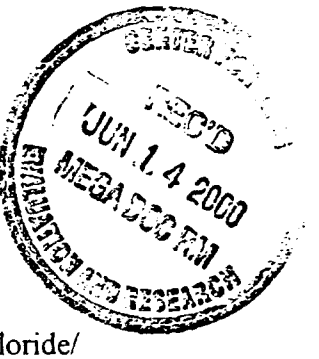
latasha Rogozenski
.ssistant Director
.egulatory Affairs

C: Yoon Kong, (HFD-550) **2 DESK COPIES** of CD-ROM AND COVER letter ıcluded

ORIGINAL

NC

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



JUN 13 2000

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

NDA 21-123
ULTRACET™
(37.5 mg Tramadol hydrochloride/
325 mg acetaminophen combination tablets)

CORRESPONDENCE
Re: FDA Change in Requirements

Dear Dr. Midthun:

Reference is made to NDA 21-123 for ULTRACET™ (tramadol hydrochloride/ acetaminophen) tablets, submitted on 31 August 1999 and to previously submitted clinical related Memorandums of Understanding (MOU) dated 14 December 1995 and 15 March 1999. Reference is also made to an "End of Review" teleconference held between FDA and The R.W. Johnson Pharmaceutical Research Institute [redacted] (RWJPRI [redacted]) on 8 June 2000 to discuss the Agency's views on the subject NDA.

During the 8 June 2000 teleconference, RWJPRI [redacted] were advised of the reviewing division's position that NDA 21-123 is not approvable because of deficiencies identified by the medical reviewer. Although we appreciate learning of the agency's views prior to receiving an action letter, the participants from RWJPRI [redacted] were shocked and dismayed that the "deficiencies" are in fact new requirements (such as providing data on 300 patients on the proposed maximum dose of 8 tablets per day for 10 days) never identified by the Agency prior to this meeting, despite multiple opportunities over the past 4-5 years. Moreover, as described below, the Agency not only did not previously reveal these new requirements, the Agency and sponsor also reached agreements on protocol design in advance of their execution.

We respectfully request that, pursuant to 21 CFR 10.75 and 314.103, the Agency schedule an urgent face to face meeting (Type A meeting) with Dr. Robert DeLap, Office Director, Office of Drug Evaluation V in attendance. The purpose of the meeting is to discuss RWJPRI's scientific and procedural objections to the "deficiencies" identified at the 8 June 2000 teleconference.

Issues to be Resolved:

(1) From the outset of the clinical program, RWJPRI [redacted] have consistently proposed, and FDA has known, (refer to 14 December 1995 Memorandum of Understanding) that ULTRACET™ would be developed and indicated for the management of [redacted] acute [redacted] pain. Further, the Agency agreed at this December 1995 meeting that the clinical program for the above noted indication would consist of the completion of two (2) single dose studies in dental pain models and one (1) multiple dose study of 4 weeks in duration. The rationale for dose selection as well as the designs and objectives of these studies were presented to the Agency. The Agency offered several comments and corrections, which RWJPRI [redacted] incorporated into the protocols prior to the conduct of the studies. Three years later, at a 7 December, 1998 Pre-NDA Clinical/PK meeting, and at the subsequent 9 February, 1999 teleconference, the Agency again agreed on the fileability of the package. (Refer to our Memorandum of Understanding dated 15 March 1999 and the Agency's meeting overheads provided to the Sponsor.)

(2) There is no public health reason to override previous agreements with RWJPRI on this product. No "substantial scientific issue essential to determining the safety or effectiveness of the drug" has been identified after the clinical trials began. ULTRACET™ is a combination of two well-known analgesics with no known pharmacokinetic or toxicologic interaction. The safety and efficacy of tramadol and acetaminophen have been well established. These two components continue to be used safely for pain management throughout the world.

(3) Despite multiple opportunities over the past 4-5 years, the Agency did not avail itself of these opportunities to communicate the new requirements until after the development program had been completed.

(4) Some of the new "requirements" fall well outside the scope of the Analgesic Guidelines and may not be clinically feasible. In addition, some of the studies suggested by the new requirements run contrary to good pain management practice.

(5) The new "requirements" are inconsistent with preapproval requirements posed for another combination analgesic, i.e., Vicoprofen (hydrocodone bitartrate/ibuprofen tablets).

Throughout the development of this combination product, we have closely collaborated with FDA, and we have fulfilled the clinical requirements per agreements with the Agency as specified in the corresponding MOUs. Further, we believe that we have showed adequate safety and efficacy of ULTRACET™ and that NDA 21-123 is approvable.

Please note that we are preparing a background package, list of proposed attendees and agenda for this meeting, which we consider to be of a most urgent nature. Therefore, we would greatly appreciate the scheduling of this important meeting prior to the July 1, 2000 PDUFA action date. If you have any questions, please contact me directly at (908) 704-4222, or use our telephone line dedicated for FDA use, (908) 704-4600.

Sincerely,

The R.W. Johnson
Pharmaceutical Research Institute

Natasha Rogozenski
Assistant Director
Regulatory Affairs

Jean O'Connor
Senior Director
Regulatory Affairs

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

NEW CORRESP
NC

JUN 1 5 2000

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

NDA 21-123
ULTRACET™
(37.5 mg Tramadol hydrochloride/
325 mg acetaminophen combination tablets)

CORRESPONDENCE
Participant List for June 8, 2000
Teleconference

Dear Sir/Madam:

Reference is made to NDA 21-123 for ULTRACET™ (tramadol hydrochloride/ acetaminophen) tablets, submitted on 31 August 1999 and to an "End of Review" teleconference held between FDA and The R.W. Johnson Pharmaceutical Research Institute, [redacted] (RWJPRI [redacted]) on 8 June 2000 to discuss the Agency's views on the subject NDA.

As requested by Dr. Yoon Kong, Project Manager, attached is a list of sponsor participants for the aforementioned teleconference. If you have any questions, please contact me at (908) 704-4222, or use our telephone line dedicated for FDA use, (908) 704-4600.

Sincerely,

Natasha Rogozneski

Natasha Rogozneski
Assistant Director
Regulatory Affairs

ORIGINAL

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

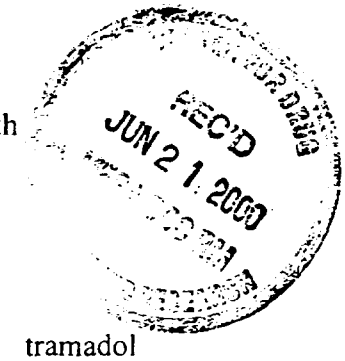
JUN 1 9 2000

NEW CORRESP
NC

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

NDA 21-123
ULTRACET™
(37.5 mg Tramadol hydrochloride/
325 mg acetaminophen combination
tablets)

CORRESPONDENCE
Request for Teleconference with
Drs. DeLap and Midthun



Dear Sir or Madam:

Reference is made to NDA 21-123 for ULTRACET™ (37.5 mg tramadol hydrochloride/325 mg acetaminophen) tablets, submitted on 31 August 1999 and to an "End of Review" teleconference held between FDA and The R.W. Johnson Pharmaceutical Research Institute [redacted] (RWJPRI [redacted] on 08 June 2000 to discuss the Agency's views on the subject NDA. Further, reference is made to correspondence sent to the Agency on 13 June 2000 requesting a Type A meeting with the Agency prior to the PDUFA action date of 01 July 2000, in order to address RWJPRI's procedural and scientific objections to the issues identified by the Agency during the 08 June teleconference. The Type A meeting has subsequently been scheduled for 6 July 2000.

Additionally, reference is made to a telephone conversation between Dr. Yoon Kong, Project Manager, and Ms. Natasha Rogozenski, RWJPRI on 19 June 2000. As requested by Dr. Kong, during that telephone discussion today, RWJPRI hereby formally requests a conference call between RWJPRI and the Agency. The purpose of this teleconference is to obtain assurance from the Agency that the action letter will not be issued prior to our 6 July 2000 meeting, and to reach mutual agreement on extending the timeclock on the review of this NDA in order to resolve the substantial issues raised on 8 June 2000. We request that Dr. Robert DeLap, Office Director ODE V; Dr. Karen Midthun, Division Director; Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products; and Dr. Yoon Kong, Project Manger, be present for this teleconference. RWJPRI attendees will be Dr. Graham Burton, Vice President, Global Clinical Research & Development; Ms. Jean O'Connor, Senior Director, Regulatory Affairs, and Ms Natasha Rogozenski, Assistant Director, Regulatory Affairs.

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As discussed with Dr. Kong earlier today, that meeting has been scheduled for Tuesday 26 June 2000 at 11:30 AM. Thank you for expeditiously arranging this teleconference. If you have any questions, please contact me at (908) 704-4222 or use our telephone line dedicated for FDA use, (908) 704-4600.

Sincerely,

The R. W. Johnson Pharmaceutical Research Institute

Natasha Rogozenski

Natasha Rogozenski
Assistant Director
Regulatory Affairs

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

NEW CORRESPONDENCE JUN 22 2000

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

NDA 21-123
ULTRACET™
(37.5 mg Tramadol hydrochloride/
325 mg acetaminophen combination
tablets)

CORRESPONDENCE
Background Document for Follow-up
Meeting Re: Scientific and Procedural
Objections to the Issues Identified by
FDA at 08 June 2000 Teleconference

Dear Dr. Midthun,

Reference is made to NDA 21-123 for ULTRACET™ (37.5 mg tramadol hydrochloride/325 mg acetaminophen) tablets, submitted on 31 August 1999 and to an "End of Review" teleconference held between FDA and The R.W. Johnson Pharmaceutical Research Institute [redacted] (RWJPRI [redacted] on 08 June 2000 to discuss the Agency's views on the subject NDA. Further. reference is made to correspondence sent to the Agency on 13 June 2000 requesting a Type A meeting with the Agency prior to the PDUFA action date of 01 July 2000.

The purpose of the meeting is to discuss and reach resolution on RWJPRI's scientific and procedural objections to the issues identified by the Agency at the 08 June 2000 teleconference. Unfortunately, this meeting has been scheduled for 06 July 2000, five days after the 01 July 2000 (10 month) PDUFA action date. Therefore. we request that the Agency extend the review clock by two months by mutual agreement per 21CFR 314.100(c). This delay would postpone the scheduled action date to the 12-month PDUFA action date of 01 September 2000, in order to resolve the substantial issues raised herein and in our 13 June 2000 letter. A separate meeting between RWJPRI and the Agency has been scheduled for 27 June 2000 to discuss the topic of an extension to the review clock.

With regard to the process. we have already pointed out in our letter of 13 June 2000 (Attachment 2). that in two meetings prior to the filing of this NDA. RWJPRI

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presented the clinical plan to the FDA, in a 1995 pre-IND and a 1998 pre-NDA meeting. On the first occasion. the studies were exhaustively described, we accepted FDA's comments, and modified the clinical plan in accordance with the comments. Minutes of that meeting were submitted to the FDA. with no response back. We had no reason to believe that the clinical development plan was not satisfactory to the Division.

Similarly, in 1998, a second meeting occurred. at which time we were informed that the clinical package was fileable, although of course the FDA could not comment on the adequacy of the data until the studies were specifically reviewed. At no time was any defect identified that would have led to the NDA's being refused for filing. Specifically, the record of communications between the sponsor and FDA attest to the fact that FDA was well aware that we were pursuing both acute [redacted] pain indications for this combination product. Certainly the absence of a "critical" study, or a flawed methodology in the chronic pain program, was never discussed. When the NDA had been accepted for filing and under review for nearly a year. we were astonished to learn that the FDA has reversed itself regarding the adequacy of the clinical program.

We emphasize the record of communications between RWJPRI and FDA because we strongly believe that the Agency had a duty. whether it was legal or regulatory. to treat these meetings as important occasions for negotiation, agreement and clarity. Had the FDA asked for additional studies, RWJPRI would have undertaken them after appropriate deliberation with FDA. It was in order to prevent these situations. and the enormous waste of private and governmental resources that accompany them. that the Food, Drug and Cosmetic Act was amended in 1998 to require that the Agency bind itself to agreements and commitments made in such meetings. Indeed. the critical meeting in 1998 was after the enactment of the statute, when the Division was in fact bound by Section 119 of FDAMA, 21 U.S.C §355(b)(4)(B).

There is no public health reason to override previous agreements with RWJPRI on this product. No "substantial scientific issue essential to determining the safety or effectiveness of the drug" has been identified after the clinical trials began. ULTRACET™ is a combination of two well-known analgesics with no known pharmacokinetic or toxicologic interaction in man. The safety and efficacy of tramadol and acetaminophen have been well established. These two components continue to be used safely for pain management throughout the world.

In light of the particular circumstances presented here, we are hopeful that the Division will thoroughly revisit and reconsider the issues raised in the 08 June teleconference. RWJPRI therefore provides this background package in preparation for the 06 July 2000 meeting. This package contains an Agenda, Sponsor Participant List and Background Information citing our scientific issues to be resolved (Attachment 1).

The enclosed Background Package addresses the scientific issues and demonstrates that RWJPRI has fulfilled the requirements of the Fixed Combination Prescription Drugs for Humans regulations per 21 CFR 300.50. Specifically, we have established that each component makes a contribution to the claimed effects of the combination and that the dosage of each component is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy. We have fulfilled all FDA requests and agreements communicated to us over the past 4-5 years (Attachment 3), to ensure that NDA 21-123 was accepted for filing and ultimately approvable. We therefore look forward to a productive meeting on July 6th.

If you have any questions, please contact Ms. Natasha Rogozenski at (908) 704-4222, Ms. Jean O'Connor at (908) 704-5121, or use our telephone line dedicated for FDA use, (908) 704-4600.

Sincerely,

The R.W. Johnson
Pharmaceutical Research Institute

Graham Burton
Vice President
Regulatory Affairs

Jean O'Connor
Senior Director
Regulatory Affairs

PARTICIPANT LIST

AGENDA

ATTACHMENT 1

DOCUMENT

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

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

NEW CORRESPONDENCE JUN 28 2000

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

NDA 21-123
ULTRACET™
(37.5 mg Tramadol hydrochloride/ 325 mg acetaminophen combination tablets)

NC

CORRESPONDENCE
References for 28 June Supplemental Information to Background Document Submitted 22 June 2000 for Follow-up Meeting Re: Scientific and Procedural Objections to the Issues Identified by FDA at 08 June 2000 Teleconference

Dear Dr. Midthun,

Reference is made to NDA 21-123 for ULTRACET™ (37.5 mg tramadol hydrochloride/325 mg acetaminophen) tablets, submitted on 31 August 1999 and to an "End of Review" teleconference held between FDA and The R.W. Johnson Pharmaceutical Research Institute [redacted] (RWJPRI [redacted]) on 08 June 2000 to discuss the Agency's views on the subject NDA. Further, reference is made to correspondence sent to the Agency on 13 June 2000 requesting a Type A meeting with the Agency prior to the PDUFA action date of 01 July 2000. The purpose of the meeting is to discuss and reach resolution on RWJPRI's scientific and procedural objections to the issues identified by the Agency at the 08 June 2000 teleconference.

Finally, reference is made to the Background Document for the 06 July meeting, submitted on 22 June 2000, and the supplemental information submitted on 28 June. In the June 28th background supplement, we made reference to two articles (Attachment 5) and stated that they would be supplied under separate cover. Attached herein are those two articles for your review with the Background Document. Please note that the author of one of the references (reference 2) was incorrectly identified as Austin, rather than Anand in the background supplement dated June 28th.

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If you have any questions, please contact Ms. Natasha Rogozenski at (908) 704-4222, Ms. Jean O'Connor at (908) 704-5121, or use our telephone line dedicated for FDA use, (908) 704-4600.

Sincerely,

The R W. Johnson
Pharmaceutical Research Institute

Jean O'Connor
Senior Director
Regulatory Affairs

Natasha Rogozenski
Assistant Director
Regulatory Affairs

Cc: Dr. Yoon Kong (HFD-550) 10 Desk Copies

NDA ORIG AMENDMENT
AL

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

NOV 14 2000

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

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

Amendment
~~Class 1 Resubmission~~ Class 2 resubmission
Complete Response to 30 June 2000
Approvable Letter: Acute Pain
Indication

Dear Sir/Madam:

Reference is made to NDA 21-123 for ULTRACET™ (37.5 mg tramadol hydrochloride/325 mg acetaminophen) tablets submitted to the Agency on 31 August 1999 and the FDA action letter for this NDA dated 30 June 2000. Reference is also made to our responses to the deficiencies cited in the June 30th letter: 22 June 2000; 28 June 2000; 10 August 2000 and 15 September 2000. Finally, reference is made to additional correspondence regarding the 30 June approvable letter submitted as follows: 13 June 2000; 05 September 2000; 19 September 2000; and 04 October 2000.

As suggested by the Agency in a letter dated 03 November 2000, provided herein is The R.W. Johnson Pharmaceutical Research Institute (RWJPRI) complete response to the 30 June 2000 Approvable letter, with regard to the acute pain indication. The response consists of a Safety Update, provided in Attachment 1, and the revised labeling for ULTRACET™ for the short-term management of acute pain based on two tablets every 4 to 6 hours, provided in Attachment 2. The chronic pain indication will be addressed separately, in the future. The deficiencies cited in the 30 June approvable letter have been addressed in the correspondences dated 22 June 2000, 28 June 2000, 10 August 2000 and 15 September 2000.

Please note that the studies reported in the safety update are ongoing blinded Phase IV studies. Therefore, data is provided for all arms of these studies, in order not to break the blinds. Since blinded data would not add any relevant information to the Integrated Summary of Safety (ISS), we conferred with the Agency, and the Agency agreed in a telephone call on 09 November 2000, that an ISS and case report forms could be omitted at this time, but the Agency might want to ask for case report forms during their review

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riod. The Safety Update (Attachment 1) includes data through 30 June 2000. We lieve that this submission qualifies as a resubmission under the provisions of the *Guidance for Industry: Classifying Resubmissions in Response to Action Letters".* dditionally, we believe this resubmission fits the criteria applicable for a Class 1 esubmission and respectfully request that the Division classify this response cordingly.

or editing purposes, a Reviewer's Aid diskette is provided in WORD 7.0, WINDOWS 7 format with the draft labeling revisions made subsequent to the Four Month Safety Update, submitted on 10 December 1999. This diskette contains both annotated and nannotated versions of the label. We have provided only Dr. Yoon Kong, Project Manager, with two copies of this diskette in her Desk Copy of this submission.

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

Sincerely,

The R.W. Johnson
Pharmaceutical Research Institute

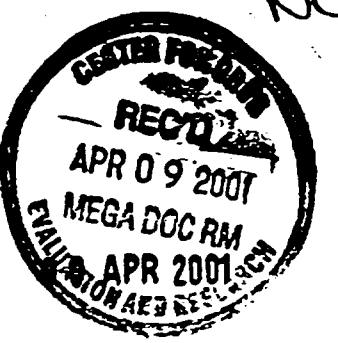
Natasha Rogozenski

Natasha Rogozenski
Director
Regulatory Affairs

cc: 15 desk copies to Yoon Kong, PharmD (HFD-550)
Two Copies of Reviewer's Aid Labeling diskette are provided in Dr. Kong's Desk Copy only

SUPPL NEW CORRESP

NC



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

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

CORRESPONDENCE:
Response to FDA Request for
Electronic copies of Proposed Labeling
for Acute Pain Indication

Dear Sir/Madam:

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

Additionally, reference is made to a telephone message from Dr. Yoon Kong, FDA, to Ms. Natasha Rogozenski on 05 April 2001, requesting three electronic copies of the labeling that we proposed in the 14 November 2000 resubmission, preferably in WORD format. As requested by the agency, three diskettes of the proposed labeling are provided. The labeling is in WORD 7.0, WINDOWS 97 format.

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

Sincerely,

Natasha Rogozenski

Natasha Rogozenski
Director
Regulatory Affairs

Cc: Yoon Kong, Pharm D (HFD-550) with (1) diskette

ORIGINAL

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

17 APR 2001

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

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

CORRESPONDENCE:
Response to FDA Request for
Information Received via Fax
on 06 April 2001

~~N~~ BM
CORRECT

Dear Sir/Madam:

Reference is made to NDA 21-123 for ULTRACET™ (37.5 mg tramadol hydrochloride/325 mg acetaminophen) tablets submitted by The R.W. Johnson Pharmaceutical Research Institute (RWJPRI) to the Agency on 31 August 1999, to the FDA action letter for this NDA dated 30 June 2000, and to RWJPRI's 15 September 2001 response to the Agency's 08 September 2001 fax request for adverse event data on subjects who took at least 7 tablets of ULTRACET for 7 or more consecutive days.

Additionally, reference is made to the agency's 06 April 2001 fax request, from Dr. Yoon Kong, for RWJPRI to provide narratives for selective patients and a comparative table of treatment emergent adverse events in patients using the comparator drug at the maximum dose for 7 days or greater. As requested by the agency, Attachment 1 includes narratives for 23 patients who presented injury and 10 patients who presented weight decrease, all of whom took at least 7 tablets of ULTRACET for 7 or more consecutive days.

Attachment 3 provides tables of treatment emergent adverse events in patients using the comparator drugs, ibuprofen or acetaminophen with codeine, at the maximum dose for 7 days or greater. An additional table provides treatment emergent adverse events in patients using tramadol with acetaminophen (TRAM/APAP) during the double-blind phase of the studies.

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ATTACHMENT 1

ATTACHMENT 2

ATTACHMENT 3

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

Sincerely,

Natasha Rogozenski

Natasha Rogozenski
Director
Regulatory Affairs

Cc: Yoon Kong, Pharm D (HFD-550)

ATTACHMENT 1

ATTACHMENT 2

ATTACHMENT 3

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

N-000/BM

27 APR 2001

NDA ORIG AMENDMENT

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

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

CORRESPONDENCE:
Response to FDA Request for Information Received via e-mail on 26 April 2001

Dear Sir/Madam:

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

Additionally, reference is made to the Agency's 26 April 2001 e-mail request from Dr. Yoon Kong, for RWJPRI to provide the number of elderly patients who received 5, 6, 7, and 8 tablets of ULTRACET a day for five days or more; the number of patients who discontinued due to adverse events (drug related or not) within the first five days of treatment, and discontinuations due to AE by body system, for elderly and non-elderly within the first five days of treatment. Our responses are attached.

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

Sincerely,

Natasha Rogozenski

Natasha Rogozenski
Director
Regulatory Affairs

cc: Yoon Kong, Pharm D. (HFD-55)

\\RARUSRARES01\PRIUSREG\ULTRAM\ULTRACET\NDA responses to FDA comments\Response to 26 APR 01 Fax - elderly.doc

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FDA Question: How many elderly patients received ULTRACET?:
8 tablets a day x 5 days or more
7 tablets a day x 5 days or more
6 tablets a day x 5 days or more
5 tablets a day x 5 days or more

RWJPRI Response:
Number of elderly patients receiving ULTRACET:

Taking at least 8 tablets a day for 5 or more consecutive days at any time during the study: 80

Taking at least 7 tablets a day for 5 or more consecutive days at any time during the study: 86

Taking at least 6 tablets a day for 5 or more consecutive days at any time during the study: 160

Taking at least 5 tablets a day for 5 or more consecutive days at any time during the study: 183

FDA Question: How many patients discontinued due to adverse events (drug related or not) within the first five days of treatment? Please provide discontinuations due to AE by body system, for elderly and non-elderly within the first five days of treatment.

RWJPRI Response:
Ninety-nine subjects discontinued due to adverse events within the first five days of treatment. A table of subjects who withdrew from the studies within the first five days of treatment is provided in Attachment 1. This table is sorted by body system, and is grouped according to elderly (≥65 yrs) and non-elderly (≤64 yrs).