

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-123

CORRESPONDENCE



THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

AUG 31 1999

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

NDA 21-123

37.5 mg Tramadol hydrochloride/
325 mg acetaminophen combination tablets

NEW DRUG APPLICATION

Dear Sir/Madam:

Reference is made to IND [] submitted 15 March 1996 and amendments to this IND which collectively have supported the development of the new combination product, 37.5 mg tramadol hydrochloride/325 mg acetaminophen tablets. Reference is also made to pre-NDA meetings or teleconferences on 2 June 1998 (Chemistry, Manufacturing and Control), 07 December 1998 and 9 February 1999 (PK/Clinical), and 22 April 1999 (Nonclinical) during which topics and agreements related to this NDA submission were discussed. Memorandums of Understanding documenting these meetings were submitted to the Agency on 3 February, 1999 (CM&C), 15 March 1999 (PK/Clinical) and 26 April 1999 (Nonclinical), respectively, by this Sponsor. No amendments to those records were requested by the Agency.

At this time, the R. W. Johnson Pharmaceutical Research Institute (RWJPRI) is submitting a NDA 21-123 supporting the safety and efficacy of this new combination product, to be indicated for the treatment of [] acute [] pain.

In accordance with §314.50(d)(5)(vii), RWJPRI is providing an abuse liability assessment package for this combination product. This information consists of two parts: first, the Drug Abuse and Overdosage section of the NDA describing experience with tramadol/acetaminophen combination relative to abuse liability and overdosage, and second, a comprehensive update on ULTRAM® (tramadol hydrochloride tablets) abuse liability. This latter update was prepared based upon agreements with the Agency to provide this information on the component drug, tramadol hydrochloride, and is being submitted at this time to the original ULTRAM® (tramadol hydrochloride tablets) NDA 20-281, as well as in this combination product NDA 21-123. Both the Drug Abuse and Overdosage section in Item 8 of NDA 21-123 addressing experience with

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tramadol/acetaminophen combination and the comprehensive update on ULTRAM® (tramadol hydrochloride tablets) abuse liability are included in Item 8 of this new NDA. Separate copies of these data are bound as desk copy volumes - one each for FDA HFD-170 and for NIDA.

Diskettes containing the annotated and running text label for this new product in Microsoft Word 7.0 format are provided with this submission as noted in the Overall Reviewers Guide (NDA Volume 1). By agreement with the Agency, an electronic review aid will be submitted on CD-ROM within two weeks of this submission date.

User Fee payment in the amount of [REDACTED] was transferred to Mellon Bank by electronic transfer, number [REDACTED] on 24 August 1999 under User Fee ID No. 3774. This will be deposited at Mellon Bank [REDACTED] on 26 August 1999. A copy of the Form FDA 3397 is provided herein.

In addition, at this time, in accordance with 21 CFR § 314.50(j), we state that this application, upon approval by the U.S. Food and Drug Administration, is entitled to a five year period of marketing exclusivity under provisions of 21 CFR § 314.108(b)(2), and respectfully request the granting of this exclusivity.

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

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

Sincerely,

The R.W. Johnson
Pharmaceutical Research Institute



Sandra Cottrell, Ph.D.
Director
Regulatory Affairs

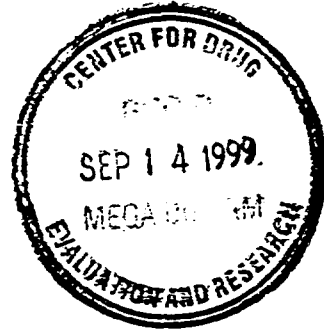


Natasha Rogozenski
Assistant Director
Regulatory Affairs

cc: Dr. Constance Lewin (HFD-550)

ORIGINAL
ORIG AMENDMENT
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THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
ROUTE 202 P.O. BOX 309 RARITAN, NEW JERSEY 08869-0602



SEP 13 1999

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

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

AMENDMENT TO PENDING NDA
NDA Electronic Review Aid- CD ROM

Dear Sir/Madam:

Reference is made to NDA 21-123 submitted 31 August 1999 for the new combination product, 37.5 mg tramadol hydrochloride/325 mg acetaminophen tablets. Reference is also made to pre-NDA meetings or teleconferences on 02 June 1998 (Chemistry, Manufacturing and Control), 07 December 1998 and 09 February 1999 (PK/Clinical), and 22 April 1999 (Nonclinical) during which topics and agreements related to this NDA submission were discussed. Memorandums of Understanding documenting these meetings were submitted to the Agency on 03 February, 1999 (CM&C), 15 March 1999 (PK/Clinical) and 26 April 1999 (Nonclinical), respectively, by this Sponsor. No amendments to those records were requested by the Agency. Amongst these agreements with the Agency was the commitment to submit an electronic review aid on CD-ROM within two weeks of the NDA submission.

At this time, the R.W. Johnson Pharmaceutical Research Institute (RWJPRI) is submitting the electronic review aid supporting NDA 21-123. Electronic copies of key sections of the NDA demonstrating the safety and efficacy of this new combination product, to be indicated for the treatment of [redacted] acute [redacted] pain are provided on the enclosed 3 CD-ROMS. Additional electronic media for this NDA consists of diskettes containing the annotated and running text label for this new product in Microsoft Word 7.0 format, which was previously provided with the paper copy of the submission.

The electronic review aid submitted at this time in Attachment 1 consists of three CD-ROMs. The first CD-ROM contains key documents from Items 1-8/10 of NDA 21-123. The second and third CD-ROM contains data sets from Item 8/10 of NDA 21-123. The specific contents of each CD ROM are listed in the Electronic Index provided on the CD-ROM (1 of 3). A total of two copies of this CD-ROM set are provided at this time - one for the archival copy and one for the Project Manager, Dr. Constance Lewin.

It is our expectation that the CD-ROM data will be transferred to a network site at the Agency. Technical assistance in this regard can be provided, should the Agency wish this support from RWJPRI.


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

Sincerely,

The R.W. Johnson
Pharmaceutical Research Institute



Sandra Cottrell, Ph.D.
Director
Regulatory Affairs



Natasha Rogozenski
Assistant Director
Regulatory Affairs

cc: Dr. Constance Lewin (HFD-550)

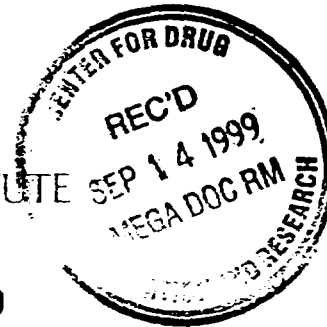
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THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 202, P.O. BOX 300, BARTON, NEW JERSEY 08669-0602



SEP 13 1999

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

NDA 21-123

37.5 mg Tramadol hydrochloride/
325 mg acetaminophen combination tablets

AMENDMENT TO PENDING NDA

NDA Electronic Review Aid- CD ROM
for NIDA and HFD-170

Dear Sir/Madam:

Reference is made to NDA 21-123 submitted 31 August 1999 for the new combination product, 37.5 mg tramadol hydrochloride/325 mg acetaminophen tablets.

At this time, the R.W. Johnson Pharmaceutical Research Institute (RWJPRI) is submitting an electronic review aid supporting the Abuse Liability Package for NDA 21-123 for NIDA and HFD-170. Enclosed is a CD-ROM containing the following items:

- Readme first.doc
- Abuse Reviewer's Guide.doc
- Tramadol Hydrochloride/Acetaminophen Combination Product Abuse and Overdosage Section from Item 8 NDA 21-123 (Drug Abuse and Overdose Information.doc, Drug Abuse and Overdose Information_Maintext.pdf and Abuse and Overdose Information_References.pdf)
- Comprehensive ULTRAM[®] Abuse Liability Review and Update Summary [EDMS-USRA-4164971;2.0] (Executive Summary Abuse.pdf and Executive Summary Abuse.doc) and Comprehensive ULTRAM[®] Abuse Liability Review and Update [EDMS-USRA-3828380;3.0] (Comprehensive Abuse Liability.doc and Liability Report-Abuse.pdf)

The reports on CD-ROM include an executive summary of the ULTRAM comprehensive abuse report with hypertext links to the expanded text portions of the comprehensive abuse review and update report. Only files with .pdf extensions contain hypertext links. Files with .doc extensions are provided to facilitate word processing access. Please note that only hard copies of the abuse report contain the appendices, as these appendices are all scanned documents without hypertext links and accordingly would be very difficult to utilize electronically. All documents contained on the CD-ROM except for the Readme first.doc were provided in the NDA and were separately volumized for NIDA and HFD-170.

total of three copies of this CD-ROM set is provided at this time – one for the archival copy, one copy for NIDA and one copy for HFD-170.

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

Sincerely,

The R.W. Johnson
Pharmaceutical Research Institute



Sandra Cottrell, Ph.D.
Director
Regulatory Affairs



Natasha Rogozenski
Assistant Director
Regulatory Affairs

cc: Dr. Constance Lewin (HFD-550)

DUPLICATE



NEW CORRESP
NC

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

SEP 14 1999



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

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

Amendment to Pending NDA Submission
Request for Deferral of Submission of
Pediatric Data

Dear Sir/Madam:

Reference is made to NDA 21-123 submitted 31 August 1999 for the new combination product, 37.5 mg tramadol hydrochloride/325 mg acetaminophen tablets.

At this time, the R. W. Johnson Pharmaceutical Research Institute (RWJPRI) is submitting an amendment to this NDA 21-123, requesting a deferral under §314.55(b)(1) regarding the submission of pediatric data supporting the safe and effective use of this product in a pediatric population. Specifically, the proposed target labeling currently provided with the NDA submission indicates under Pediatric Use that the, "use of this product is not recommended because safety and efficacy in patients under 16 years of age have not been studied."

RWJPRI requests a deferral under §314.55(b)(1) pending assessment of the data from the ongoing clinical program for ULTRAM® (tramadol hydrochloride tablets). ULTRAM is one of the two components of this new combination product and has currently not been approved for use in pediatric subjects, although the other component, acetaminophen, has significant data documenting its use in pediatrics. RWJPRI believes it is appropriate to assess the ULTRAM pediatric data from those ongoing studies before designing pediatric studies with the combination product. Upon completion of the ULTRAM pediatric program, RWJPRI proposes to provide the Agency with a strategy to support addressing use of this new combination product in pediatric subjects. We anticipate that such a proposal would be made to the Agency during their ongoing review of this NDA 21-123 and certify to work with the Agency to define, and as appropriate implement, such strategy with due diligence. Information on the current and pending ULTRAM pediatric studies, and various documents surrounding the ULTRAM pediatric program are provided by cross reference to NDA 20-281 ULTRAM® (tramadol hydrochloride tablets) and IND (tramadol hydrochloride tablets and capsules).



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

Sincerely,

The R. W. Johnson
Pharmaceutical Research Institute

Sandra Cottrell, Ph.D.
Director
Regulatory Affairs

Natasha Rogozenski
Assistant Director
Regulatory Affairs

cc: Dr. Constance Lewin (HFD-550)



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NEW CORRESP

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THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

OCT 5 1999

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

NDA 21-123
37.5 mg Tramadol hydrochloride/
325 mg acetaminophen combination tablets
AMENDMENT TO PENDING NDA
NDA Electronic Review Aid- CD-ROM
for NIDA and HFD-170
Replacement CD-ROM

Dear Sir/Madam:

Reference is made to NDA 21-123 submitted 31 August 1999 for the new combination product, 37.5 mg tramadol hydrochloride/325 mg acetaminophen tablets and to the NDA Electronic Review Aid submitted on 13 September 1999.

At this time, The R.W. Johnson Pharmaceutical Research Institute (RWJPRI) is submitting a replacement electronic review aid supporting the Abuse Liability Package for NDA 21-123 for NIDA and HFD-170. As a consequence of systems upgrading, the reports on the CD-ROMs provided to the Agency on 13 September 1999 were noted to have lost internal pagination and suffered a version error. Accordingly, the reports on the replacement CD-ROM contain the same contents as previously submitted with corrected internal pagination and were corrected to include the most current version of the reports, consistent with the hard copies of these reports submitted with NDA 21-123 and NDA 20-281 on 31 August 1999. The contents of the CD-ROM are restated below.

- Readme first.doc
- Abuse Reviewer's Guide.doc
- Tramadol Hydrochloride/Acetaminophen Combination Product Abuse and Overdosage Section [EDMS-USRA-4220035:2.0] from Item 8 NDA 21-123 (Drug Abuse and Overdose Information.doc, Drug Abuse and Overdose Information_Maintext.pdf and Abuse and Overdose Information_References.pdf)
- Comprehensive ULTRAM[®] Abuse Liability Review and Update Summary [EDMS-USRA-4164971:2.0] (Executive Summary Abuse.pdf and Executive Summary Abuse.doc) and Comprehensive ULTRAM[®] Abuse Liability Review and Update [EDMS-USRA-3828280:3.0] (Comprehensive Abuse Liability.doc and Liability Report-Abuse.pdf)

As previously noted, the reports on CD-ROM include an executive summary of the ULTRAM comprehensive abuse report with hypertext links to the expanded text portions of the comprehensive abuse review and update report. Only files with .pdf extensions contain hypertext links. Files with .doc extensions are provided to facilitate word processing access. All documents contained on the CD-ROM except for the Readme first.doc were provided in the NDA and were separately volumized for NIDA and HFD-170.

A total of three copies of the replacement CD-ROM is provided at this time – one for the archival copy, one copy for NIDA and one copy for HFD-170. The previous version of this CD-ROM is obsolete and should be destroyed.

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

Sincerely,

The R.W. Johnson
Pharmaceutical Research Institute



Sandra Cottrell, Ph.D.
Director
Regulatory Affairs



Natasha Rogozenski
Assistant Director
Regulatory Affairs

cc: Dr. Constance Lewin (HFD-550)

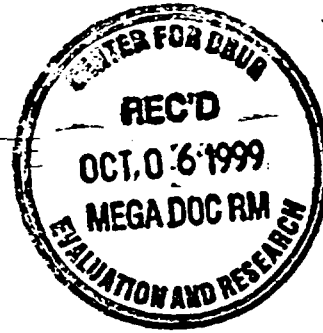
ORIGINAL

NEW CORRESP

NC

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 002, P.O. BOX 000, RARITAN, NEW JERSEY 08869-0002



OCT 5 1999

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

NDA 21-123

37.5 mg Tramadol hydrochloride/
325 mg acetaminophen combination tablets

AMENDMENT TO PENDING NDA

NDA Electronic Review Aid – CD-ROM
Replacement CD-ROM (1 of 3)

Dear Sir/Madam:

Reference is made to NDA 21-123 submitted 31 August 1999 for the new combination product, 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.

As a consequence of systems upgrading, the reports contained on the first CD-ROMs (1 of 3) provided to the Agency on 13 September 1999 were noted to have lost internal pagination and in some cases suffered a version error. Accordingly, the reports on the replacement CD-ROMs include the same reports contained on the original CD-ROMs with internal pagination correction and were corrected to include the most current version of the reports with version discrepancy, consistent with the hard copies submitted with NDA 21-123 on 31 August 1999. The first CD-ROM in this set contains key documents from Items 1-8/10 of NDA 21-123. At this time, The R.W. Johnson Pharmaceutical Research Institute (RWJPRI) is submitting a replacement for the first CD-ROM of the set (1 of 3).

The specific contents of each CD-ROM are listed in the Electronic Index provided on the first CD-ROM (1 of 3). Two copies of this replacement CD-ROM (1 of 3) are provided at this time – one for the archival copy and one for the Project Manager, Dr. Constance Lewin. The previous version of the first CD-ROM (1 of 3) is obsolete and all copies of the first volume CD-ROM should be destroyed (volumes 2 and 3 are not to be destroyed, please).

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

Sincerely,

The R.W. Johnson
Pharmaceutical Research Institute



Sandra Cottrell, Ph.D.
Director
Regulatory Affairs



Natasha Rogozenski
Assistant Director
Regulatory Affairs

cc: Dr. Constance Lewin (HFD-550)



THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 202, P.O. BOX 100, RAPTAN, NEW JERSEY 08869-1002



ATTACHMENT 1

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
37.5 mg Tramadol hydrochloride
325 mg acetaminophen combination tablets

Amendment to Pending NDA Submission
Response to Agency Requests: Additional
CMC Information and Expanded **DRUG AMENDMENT**
Submission Index

BC

Dear Sir/Madam:

Reference is made to NDA 21-123 submitted 31 August 1999 for the new combination product, 37.5 mg tramadol hydrochloride/325 mg acetaminophen tablets and to a discussion with Mr. Anthony Zeccola on 20 October 1999 regarding additional requests in support of this submission.

At this time, the R. W. Johnson Pharmaceutical Research Institute (RWJPRI) is submitting an amendment to NDA 21-123, responding specifically to clarify the address for the manufacturer of acetaminophen (manufacture site as well as administrative headquarters). This information is included in Attachment 1 of this NDA amendment and includes a replacement page to the Item 4 Technical CMC Section, as presented in Overall NDA Volume 10 (of 380)/Item 4/ Item Volume 1/ Page 8. In addition, Attachment 1 contains an updated DMF cross reference letter for [redacted] the supplier of acetaminophen for the manufacture of this combination product.

The second component of this NDA Amendment is provided in response to Dr. Hyde's request to have an Overall NDA Volume Index. Accordingly, RWJPRI is submitting an expanded submission Index (Attachment 2). This NDA Index contains an identical breakdown of the components of the NDA as submitted on 31 August 1999, but has been expanded to also identify for each entry the Overall NDA Volume, in addition to the current presentation of Item Volume/Page. The Indexing as provided in the original filing is created by the document publishing tool used by RWJPRI. We have taken the generated Index for each NDA Item as published, and manually typed a column containing the Overall NDA Volume(s) for each indexed item. In making this expansion to each Item's index, the page breaks of the index may have been altered, but there is no change in NDA components listed within the index for each item.

NAS. [unclear] 11/2/99
J. Hyde

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Lastly, RWJPRI acknowledges that the reviewing chemist, Dr. Ho, has some additional information he wishes to see regarding the statistical analysis of stability data. Dr. Ho was not available during the 20 October 1999 teleconference. It was agreed that RWJPRI would respond to this request when Mr. Zeccola is able to clarify the nature of Dr. Ho's request.

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

Sincerely,

The R.W. Johnson
Pharmaceutical Research Institute



Sandra Cottrell, Ph.D.
Director
Regulatory Affairs



Natasha Rogozenski
Assistant Director
Regulatory Affairs

cc: Mr. Anthony Zeccola (HFD-550)

ITEM 1: INDEX

Item 2



THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

NOV 29 1999

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

NDA 21-123
37.5 mg Tramadol Hydrochloride/
325 mg Acetaminophen Combination Tablets

Amendment to Pending

NDA Submission
Response to Agency Requests: Statistical
Analysis of Stability Data

COPIE AMENDMENT

BC

Dear Sir/Madam:

Reference is made to NDA 21-123 submitted 31 August 1999 for the new combination product, 37.5 mg tramadol hydrochloride/325 mg acetaminophen tablets and to a discussion with Mr. Anthony Zeccola on 08 November 1999 regarding additional requests in support of this submission.

Specifically, in NDA Item 4, Volume 1, section 3.9.4 (page 135), reference is made to "a statistical analysis of stability data". During the 08 November 1999 teleconference, Dr. Ho asked to be provided with the full report for the statistical analysis of stability data for 37.5 mg tramadol hydrochloride/325 mg acetaminophen tablets which supports the proposed expiration dating. At this time, The R.W. Johnson Pharmaceutical Research Institute (RWJPRI) is submitting an amendment to NDA 21-123, responding to Dr. Ho's request.

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

Sincerely,

Sandra Cottrell, Ph.D.
Director
Regulatory Affairs

Natasha Rogozenski
Assistant Director
Regulatory Affairs

cc: Mr. Anthony Zeccola (HFD-550)

ORIGINAL

ATTACHMENT 1



SU

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0302



DEC 10 1999

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

NDA 21-123
ULTRACET™
37.5 mg Tramadol hydrochloride
325 mg acetaminophen combination tablets
Amendment to Pending NDA Submission
Four Month Periodic Safety Update

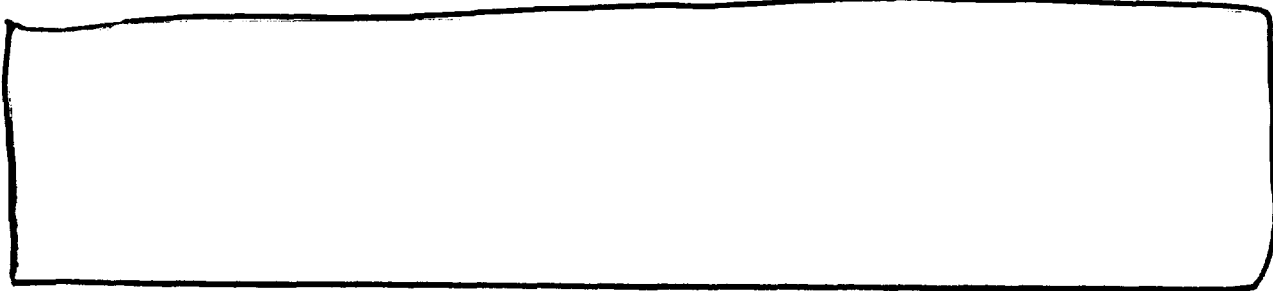
ORIGINAL

Dear Sir/Madam:

Reference is made to NDA 21-123 submitted 31 August 1999 for the new combination product, 37.5 mg tramadol hydrochloride/325 mg acetaminophen tablets, 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, and to the subsequent replacement for the first CD-ROM of the set (1 of 3) submitted 05 October 1999. (This latter submission corrected technical aspects of the disk and did not change data.)

At this time, in accordance with 21CFR314.50(d)(5)(vi)(b)(1), the R. W. Johnson Pharmaceutical Research Institute (RWJPRI) is submitting an amendment to this NDA 21-123, providing a four month safety update to this pending application. A CD-ROM, representing Volume 4 of the CD-ROM set, is also provided and contains both PDF and WORD versions of the documents it contains. A full description of the contents of the CD-ROM can be found within the overall reviewers guide provided within Volume 1 of the amendment. Volume 1 of this submission also contains the CD-ROM.

Specific reference is also made to the telephone message from the Project Manager, Mr. Tony Zeccola on November 18, 1999 indicating that the Agency, in consult with the Office of Postmarketing Drug Risk Assessment (OPDRA), was accepting the proposed tradename, ULTRACET™. Accordingly, this tradename will be utilized in this four-month safety update.



CERTIFICATION
DISCLOSURE
REVIEWER'S GUIDE



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

Sincerely,

The R.W. Johnson
Pharmaceutical Research Institute

Sandra Cottrell, Ph.D.
Director
Regulatory Affairs

Natasha Rogozenski
Assistant Director
Regulatory Affairs

cc: Mr. Anthony Zeccola (HFD-550)
Ms. Yoon Kong (HFD-550)



THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

JAN 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

GENERAL CORRESPONDENCE
Response to Biopharmaceutics Reviewer's
comments dated 12/23/99

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 comments dated 23 December 1999 from the Biopharmaceutics Reviewer regarding NDA 21-123.

At this time, The R.W. Johnson Pharmaceutical Research Institute (RWJPRI) is submitting, in duplicate, a response to the Biopharmaceutics Reviewer's comments. Data files for this response are included on the enclosed CD-ROM.

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)



THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

JAN 15 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
9201 Corporate Boulevard
Rockville, Maryland 20850

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

REVIEWER DESK COPIES:
FOR YOON KONG
PREVIOUSLY SUBMITTED
ELECTRONIC REVIEW AID-
CD ROMS- NOT FOR ARCHIVE

Attn: Yoon Kong, PharmD (HFD-550)

Dear Dr. Kong:

Reference is made to NDA 21-123 submitted 31 August 1999 for the new combination product, 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. Additionally, reference is made to the October 5, 1999 submission of a replacement for the first (1 of 3) of the CD ROMs provided on September 13. As a consequence of systems upgrading, the reports contained on the first CD-ROM were noted to have lost internal pagination and in some cases suffered a version error. Accordingly, the reports on the replacement CD-ROMs included the same reports contained on the original CD-ROMs with internal pagination correction and were corrected to include the most current version of the reports with version discrepancy, consistent with the hard copies submitted with NDA 21-123 on 31 August 1999.

At this time, as discussed with you on February 14, and 15, 2000, The R.W. Johnson Pharmaceutical Research Institute (RWJPRI) is providing you with three additional sets of three CD ROMs. These represent additional **DESK COPIES** of the October 5th replacement for the first CD ROM (which was noted as 1 of 3), and copies of the two CD ROMs (2 of 3 and 3 of 3) which were submitted on 13

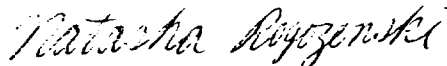
September 1999. Two sets are **DESK COPIES** for you, the other set is for the Electronic Document Room to network for reviewers.

Additionally, as we discussed on February 15, 2000, we are providing two additional **DESK COPIES** of the CD ROMs which were submitted on December 10, 1999 in the Four Month Safety Update. This CD ROM contains the updated labeling. One copy is your **desk copy**, the other copy is for the Electronic Document Room to copy to the network server for the reviewers.

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

Sincerely,

The R.W. Johnson
Pharmaceutical Research Institute



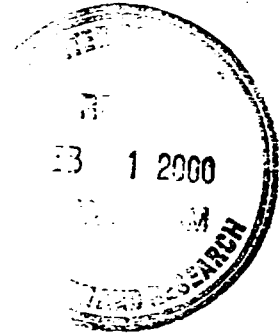
Natasha Rogozenski
Assistant Director
Regulatory Affairs

CC: Electronic Document Room
1 set of 3 CD ROMs
1 CD ROM (Four Month Safety Update)



THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 202, P.O. BOX 300, PARITAN, NEW JERSEY 08666-0302



JAN 31 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

Additional CD ROM copies for Response
to Biopharmaceutics Reviewer's
comments dated 12/23/99

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 comments dated 23 December 1999 from the Biopharmaceutics Reviewer regarding NDA 21-123, and to our reply, submitted 13 January 2000, wherein The R.W. Johnson Pharmaceutical Research Institute (RWJPRI) submitted, in duplicate, a response to the Biopharmaceutics Reviewer's comments. Data files for this response were included in duplicate on CD-ROM.

On 28 January 2000, Dr. Yoon Kong notified RWJPRI via voice mail that the CD ROMs were not received. We conducted an investigation and have confirmed that our file copies (duplicates of what was submitted to the Agency) contained the CD ROM and the courier service confirmed delivery of the package at 9:58 AM on 14 January 2000. The package was signed for by T. Jennings. At this time, as promised to Dr. Kong, we are enclosing two additional copies of the CDs containing data files provided in the 13 January response.

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: (cover letter) Yoon Kong, PharmD (HFD-550)

N:\ULTRAM\ULTRACET Tramadol APAP\NDA responses to FDA comments\response PKPD comments of 122399\response PkPD comments of 122399 Replacement CD ROM.doc

NDA 21-123

FEB 7 2000

The R. W. Johnson Pharmaceutical Research Institute
920 Route 202 South
P.O. Box 300
Raritan, New Jersey 08869-0602

Attention: Natasha Rogozenski
Assistant Director, Regulatory Affairs

Dear Ms. Rogozenski:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Ultracet™ (tramadol HCl/acetaminophen) 37.5 mg/325 mg tablets

Therapeutic Classification: Standard (S)

Date of Application: August 31, 1999

Date of Receipt: September 1, 1999

Our Reference Number: NDA 21-123

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on October 31, 1999 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be July 1, 2000 and the secondary user fee goal date will be September 1, 2000.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
Attention: Division Document Room
NUMBER
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
Attention: Division Document Room
NUMBER
9201 Corporate Blvd.
Rockville, Maryland 20850-3202

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

Sincerely,

A handwritten signature in black ink, appearing to read "LSI" with a small mark above the "I".

Leslie Vaccari
Acting Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 102, P.O. BOX 300, BARITAN, NEW JERSEY 08869-0300

NDA ORIG

MAR - 2 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

**SUBMISSION OF ELECTRONIC
CHEMISTRY, MANUFACTURING
AND CONTROLS INFORMATION**

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 request from Dr. Bart Ho on 28 February 2000 to provide an electronic copy of the main text of the Chemistry, Manufacturing and Controls (CMC) section of the NDA. At this time, we are providing the CD-ROM containing the main text of the CMC section (excluding batch documentation, Item 4B Samples, and Item 4C Methods Validation) in WORD format, and attachments in either WORD or PDF format. Attached is an index of the specific CMC information we are providing electronically. Please note that the index contains the original pagination from the NDA. However, the CD-ROM does not contain pagination since the page numbers are applied at the time of publishing when the files are converted to PDFs.

Three copies of the CD-ROM are included for distribution as follows:

- One copy for Electronic Document Control Room
- One archival copy
- One desk copy to Dr. Bart Ho, Chemistry Reviewer

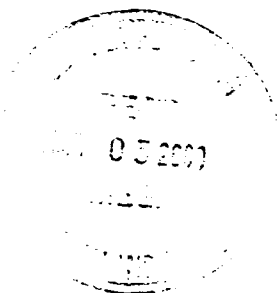
Should you have any questions or require further information, please contact me directly at (908) 704-4222 or our telephone number dedicated for FDA use at (908) 704-4600.

Sincerely,

Peggy Ferone

Natasha Rogozenski
Assistant Director
Regulatory Affairs

ORIGINAL



cc: (cover letter) Yoon Kong, PharmD (HFD-550)

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THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602



MAR - 3 2000

BS

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

Response to Statistical Reviewer's
Request Dated February 29, 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 request from Dr. Yoon Kong, Project Manager, relaying the Statistical Reviewer's request for information and clarification. The questions presented by the reviewer are listed in Attachment 1, followed by The R.W. Johnson Pharmaceutical Research Institute (RWJPRI) responses.

Three copies of a CD-ROM containing data in response to Question 1 are included for distribution as follows:

- One copy for Electronic Document Control Room
- One archival copy
- One desk copy to the Statistical Reviewer

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

Sincerely,

Peggy Ferrone

for Natasha Rogozenski
Assistant Director
Regulatory Affairs

cc: (cover letter) Yoon Kong, PharmD (HFD-550)

ORIGINAL

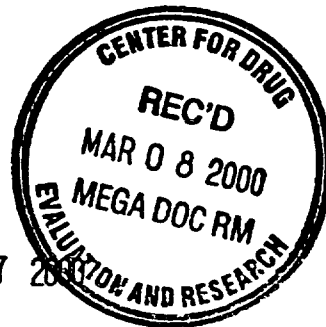


NEW CORRESP

NC

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602



MAR - 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

Review Copies-Clinical Study
Information for TRAMAP-ANAG-010,
TRAMAP-ANAG-012, and TRAMAP-
ANAG-013

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 request from Dr. Tony Carreras on 25 February 2000 to provide a review copy of specific information related to pivotal clinical studies TRAMAP-ANAG-010, TRAMAP-ANAG-012 and TRAMAP-ANAG-013 which is needed by FDA for clinical site audits. Copies of information previously submitted in the NDA are provided herein for the following investigators and clinical sites:

Protocol	Investigator	Site Address
TRAMAP-ANAG-010	Theodore A. Kiersch, BS, DDS	Cranial Pain Research 801 North Wilmot Rd. Suite E-2 Tucson, AZ 85711
		Cranial Pain Research 4028 La Linda Way Sierra Vista, AZ 85635
TRAMAP-ANAG-012	Boyd J. Tomasetti, BA, DMD	Rocky Mountain Oral and Maxillofacial Surgery, PC 6767 S. Broadway, Suite 6 Littleton, CO 80122
		Effective 08 March 00, new address for this investigator is: 7889 South Lincoln Blvd. Littleton, CO 80122

DUPLICATE

Protocol
TRAMAP-ANAG-013

Investigator
James R. Fricke, Jr., DDS, MSD

Site Address
PPD Pharmaco, Inc.
Dental Center
1510 West 34th St., Suite 100*
Austin, TX 78705

Austin Oral and Maxillofacial Surgery
259 East Colorado
LaGrange, TX 78945

*Denotes new address for this site. Investigator moved office location after NDA submission.

The following information is contained in three separate volumes (one per protocol), as requested by Dr. Carreras:

- Clinical protocol and latest amendments for each study
- Data listing of efficacy endpoints for each site
- All adverse experiences at these sites
- Discontinued patients and the reason for discontinuation
- 1-5 randomly selected completed CRF's per site

At this time we are providing the requested information with the following clarification:

- Primary efficacy endpoints were discussed with FDA at a meeting on 28 November 1995 [see Draft Memorandum of Understanding submitted to NDA 20-281 on 14 December 1995 and correspondence to IND submitted on 07 June 1996 (serial no. 010)]. At that time, FDA indicated that multiple variables would be considered by FDA in their review, as opposed to a single primary endpoint. Consequently, we are providing data listings for all efficacy endpoints for each study, as submitted in the NDA.
- In the original NDA, CRF's were submitted for all subjects who died, discontinued therapy due to an adverse event, or who had a serious adverse event. We have provided copies of five CRF's for subjects in Protocol TRAMAP-ANAG-010 randomly selected from those submitted in the NDA. No CRF's were filed in the NDA for studies TRAMAP-ANAG-012 and TRAMAP-ANAG-013, since there were none that fit those classifications. At this time, we are providing five CRF's for each of these studies randomly selected from our files. Please note that these CRF's have not been previously submitted to the NDA.
- The protocol amendment history page for clinical study TRAMAP-ANAG-012 was not included in the original NDA. For your convenience, we have included the history page along with the latest protocol amendment in Volume 2 of this submission.

Attached is the overall index to the review copies. Please note that copies of the requested information contain the original pagination filed in the NDA. Two copies of the requested information are being submitted; one for archival purposes and one review copy for Dr. Carreras.

Should you have any questions or require additional information, please contact me directly at (908) 704-4222 or our telephone 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: (cover letter) Yoon Kong, PharmD (HFD-550)
Review copy for Dr. Carreras (HFD-47)



THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602



MAR 17

ES

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
Comments Dated 10 March 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 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.

At this time, the R.W. Johnson Pharmaceutical Research Institute (RWJPRI) is submitting responses to the questions presented in the 10 March fax from the Agency. Please note that the headings in the fax comments were identified as "A. Population PK analysis in patients," and "A. Population PK/PD analysis". For ease of reference, we identify the second set as "B".

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

Sincerely,

for
Natasha Rogozenski
Assistant Director
Regulatory Affairs

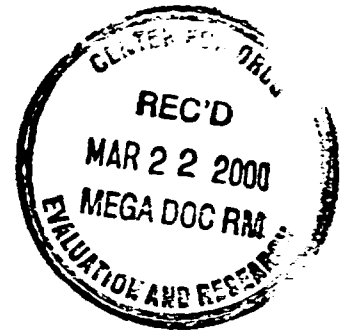
ORIGINAL

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



MAR 21 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)
9201 Corporate Boulevard
Rockville, Maryland 20850

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

NOT FOR ARCHIVES

DESK COPY for Yoon Kong -

**Previously submitted NDA Electronic
Review Aid- CD-ROM
for NIDA and HFD-170
Replacement CD-ROM**

Attn: Yoon Kong (HFD-550)

Dear Dr. Kong:

Reference is made to NDA 21-123 submitted 31 August 1999 for the new combination product, 37.5 mg tramadol hydrochloride/325 mg acetaminophen tablets and to the NDA Electronic Review Aid submitted on 13 September 1999. On October 5, The R.W. Johnson Pharmaceutical Research Institute (RWJPRI) submitted a replacement electronic review aid supporting the Abuse Liability Package for NDA 21-123 for NIDA and HFD-170. As a consequence of systems upgrading, the reports on the CD-ROMs provided to the Agency on 13 September 1999 were noted to have lost internal pagination and suffered a version error. Accordingly, the reports on the replacement CD-ROM contained the same contents as previously submitted with corrected internal pagination and were corrected to include the most current version of the reports, consistent with the hard copies of these reports submitted with NDA 21-123 and NDA 20-281 on 31 August 1999.

At this time, as discussed with you on 15 March 2000, we are providing a **DESK COPY** of the CD ROM for you. The contents of the CD-ROM are restated below.

- Readme first.doc
- Abuse Reviewer's Guide.doc
- Tramadol Hydrochloride/Acetaminophen Combination Product Abuse and Overdosage Section [EDMS-USRA-4220035:2.0] from Item 8 NDA 21-123 (Drug Abuse and Overdose Information.doc, Drug Abuse and Overdose Information_Maintext.pdf and Abuse and Overdose Information_References.pdf)

ORIGINAL

- Comprehensive ULTRAM® Abuse Liability Review and Update Summary [EDMS-USRA-4164971:2.0] (Executive Summary Abuse.pdf and Executive Summary Abuse.doc) and Comprehensive ULTRAM® Abuse Liability Review and Update [EDMS-USRA-3828280:3.0] (Comprehensive Abuse Liability.doc and Liability Report-Abuse.pdf)

The reports on CD-ROM include an executive summary of the ULTRAM comprehensive abuse report with hypertext links to the expanded text portions of the comprehensive abuse review and update report. Only files with .pdf extensions contain hypertext links. Files with .doc extensions are provided to facilitate word processing access. All documents contained on the CD-ROM except for the Readme first.doc were provided in the NDA and were separately volumized for NIDA and HFD-170.

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

Sincerely,

The R. W. Johnson
Pharmaceutical Research Institute



Natasha Rogozenski
Assistant Director
Regulatory Affairs

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



NDA 0210 AMENDMENT
MAR 23 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 Medical Reviewer
Request Dated 24 February 2000

BM

Dear Sir/Madam:

Reference is made to NDA 21-123 for ULTRACET™ 37.5 tramadol hydrochloride/325 acetaminophen combination tablets, submitted to the Agency on 31 August 1999. Reference is also made to a fax from the Agency dated 25 February 2000 wherein several requests from the Medical Reviewer (dated 2/24/00) for this NDA were presented. In follow-up to this request, The R.W. Johnson Pharmaceutical Research Institute requested and was granted a teleconference on 01 March 2000 with the Medical Reviewer and the Project Manager, in order to clarify some of the comments presented in the fax. The Agency requested responses by 24 March 2000. Accordingly, attached are our responses.

The Reviewer comment is provided for each item. Where appropriate, agreements reached with the Agency during 01 March 2000 teleconference are also stated. The 25 February 2000 fax numbered the first three items "1". The Agency agreed to re-numbering these items as "1a, 1b and 1c".

As requested by the Project Manager during a 28 February 2000 telephone discussion, we are submitting the response both in hard copy and on CD-ROM. Four copies of the CD-ROM are provided: one for the Central Document Room archive, and three DESK COPIES for the Project Manager and the reviewer. The CD-ROM includes a README.DOC file and an Index of the electronic files.

DUPLICATE

Should you have any further questions, please contact me directly at (908) 704-4222 or at 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) (3 DESK COPIES)



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

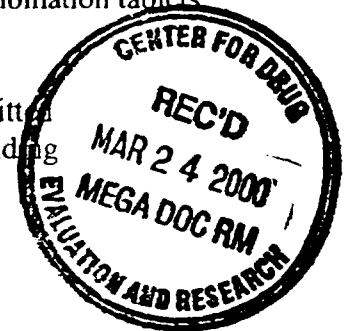
MAR 23 2000

NEW COPY

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
37.5 mg Tramadol hydrochloride/
325 mg acetaminophen combination tablets

CORRESPONDENCE
Copies of Previously Submitted
Memorandum of Understanding



NC

Dear Sir/Madam:

Reference is made to NDA 21-123 for ULTRACET™ (tramadol hydrochloride/acetaminophen) tablets, submitted on August 31, 1999. Reference is also made to a voice mail request on March 13, 2000 from Dr. Yoon Kong, Project Manager, requesting copies of Memorandum of Understanding submitted within the past three years for tramadol/acetaminophen. In response, attached are copies of correspondence submitted as follows:

<u>Date of Submission</u>	<u>Subject of Meeting</u>
December 14, 1995	Discussion of Overall Development Plan for filing an IND and NDA
February 3, 1999	Pre-NDA CM&C Teleconference
March 15, 1999	Pre-NDA Clinical/PK Program and Subsequent Follow-up Teleconference
April 26, 1999	Pre-NDA Preclinical Program Teleconference

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

Sincerely,

Natasha Rogozenski

Natasha Rogozenski
Assistant Director
Regulatory Affairs

DUPLICATE

cc: Dr. Yoon Kong (HFD-550)



THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

MAR 30 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 Comments Relating to
17 March 2000 Amendment **23**

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. Reference is also made to the responses provided on March 17, and to telephone messages from the Project Manager, Dr. Yoon Kong, to Ms. Natasha Rogozenski, (The R.W. Johnson Pharmaceutical Research Institute) on 21 and 24 March 2000. Specifically, on 21 March 2000, Dr. Kong communicated that upon reviewing our responses submitted on 17 March 2000, the Biopharmaceutics Reviewer stated that we were missing data requested in the 10 March 2000 fax relating to the inclusion of the active metabolite M1 in the PK/PD analysis. On 22 March 2000, Ms. Rogozenski clarified that the original request did not specify inclusion of the active metabolite M1 in the PK/PD analysis and offered to submit our rationale as to why it was not performed. Finally, on 24 March 2000, Dr. Kong communicated that the Biopharmaceutics Reviewer would like a detailed explanation as to why this active metabolite M1 was omitted from the PK/PD analysis.

At this time, in response to the 21 and 24 March 2000 requests, we are providing our rationale for not including the active metabolite M1 in our PK/PD analysis.

ORIGINAL

ULTRACET™ NDA RESPONSES TO FDA COMMENTS/RESPONSE TO BIOPHARM REVIEWER RE METABOLITES CVR 21-123