

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-123**

**APPROVAL LETTER**



NDA 21-123

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

Dear Ms. Rogozenski:

Please refer to your new drug application (NDA) dated November 14, 2000, received November 15, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ultracet (325 mg acetaminophen/37.5mg tramadol hydrochloride) tablets.

We acknowledge receipt of your submissions dated June 14 (2), July 16, August 9, August 13, and August 14, 2001. Your submission of June 14, 2001 constituted a complete response to our May 15, 2001 action letter.

This new drug application provides for the use of Ultracet (acetaminophen/tramadol) tablets for the short-term management of acute pain.

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

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

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-123." Approval of this submission by FDA is not required before the labeling is used.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

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). We note that you have not fulfilled the requirements of 21 CFR 314.55 (or 601.27). We are waiving studies in children zero to two years of age. We are deferring submission of your pediatric studies for children two to 16 years of age until January 1, 2002. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate. 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 notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 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](http://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.

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

Division of Drug Marketing, Advertising, and Communications, HFD-42  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857

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

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

If you have any questions, call Mary Jane Walling, at (301) 827-2268.

Sincerely,

*{See appended electronic signature page}*

Lawrence Goldkind, M.D.  
Deputy Division Director  
Division of Anti-Inflammatory, Analgesic, and  
Ophthalmic Drug Products, HFD-550  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research

Enclosure

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-123**

**APPROVABLE LETTER**



Food and Drug Administration  
Rockville MD 20857

NDA 21-123

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

JUN 30 2000

Dear Ms. Rogozenski :

Please refer to your new drug application (NDA) dated August 31, 1999, received September 1, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ultracet Tablets (tramadol hydrochloride/acetaminophen tablets) 37.5 mg /325 mg.

We acknowledge receipt of your submissions dated September 13 (two) and 14, October 5 (two) and 22, November 29, December 10, 1999, January 13, 15 and 31, March 2, 3, 7, 17, 21, 23 (two) and 30, April 3, 7, 13, 20 and 28, May 1, 3 and 12, June 13, 15, 19, 22 and 28 (two) 2000.

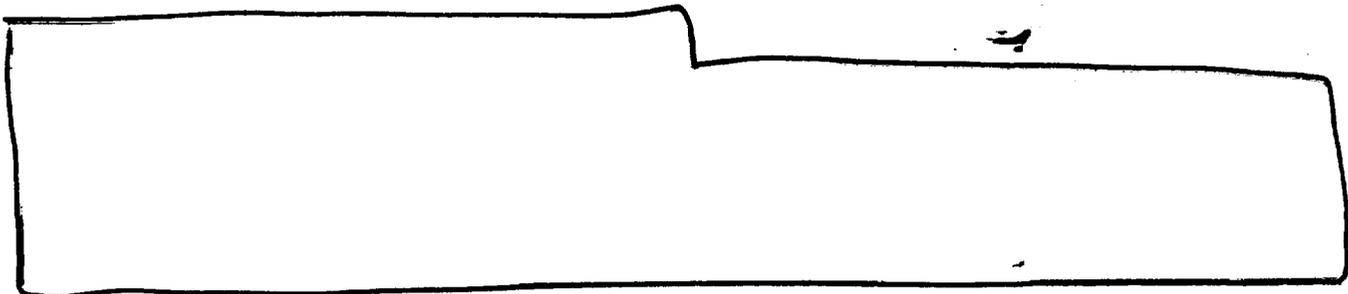
This new drug application proposes an indication for the management of [redacted] acute [redacted] pain.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

With regard to short-term management of acute pain:

1. The data do indicate a contribution of each component in the combination product, tramadol/acetaminophen, to the claimed effect (i.e., treatment of acute pain) in the dental pain model. Further characterization of multiple-dose effects and dose-response relationships is needed to support the dosing recommendations. Issues which need to be addressed are as follows:
  - a. the effect of a single tablet dose in acute pain
  - b. the utility of the 2-tablet dose in the treatment of non-dental acute pain conditions (e.g., post-surgical)
  - c. short-term multiple dose effect

2. The adequacy of the current safety database will depend upon the dosing recommendation that is established for the treatment of acute pain.



Inspections of the manufacturing facilities for your NDA are ongoing. We remind you that the facilities, controls for the manufacturing, processing, packing and holding of the drug substance and drug product must be in compliance with the current good manufacturing practice regulations as described in 21 CFR 210 and 211.

Labeling comments are deferred until above comments have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with this Division to discuss what further steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

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

Sincerely,

*/S/*

Karen Midthun, M.D.  
Director  
Division of Anti-Inflammatory, Analgesic and  
Ophthalmic Drug Products  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research