CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 75-962

Name: Tramadol Hydrochloride Tablets, 50 mg

Sponsor: Watson Laboratories, Inc.

Approval Date: June 24, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-962

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-962

APPROVAL LETTER

ANDA 75-962

JUN 24 2002

Watson Laboratories, Inc.
Attention: Ernest E. Lengle, Ph.D.
311 Bonnie Circle
Corona, CA 92880

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated September 1, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Tramadol Hydrochloride Tablets, 50 mg.

Reference is also made to the Approvable Letter issued by this Office on January 15, 2002, and to your amendments dated December 4, 2000, and June 13, 2002.

The listed drug product (RLD) referenced in your application, Ultram Tablets, 50 mg, of R.W. Johnson Pharmaceutical Research Institute, is subject to a period of patent protection which expires on April 12, 2020 (U.S. Patent No. 6,339,105). Your application contains a statement under Section 505(j)(2)(A) of the Act and 21 CFR 314.94(a)(12)(iii)(A) stating that U.S. Patent No. 6,339,105 is a method of use patent, and that your labeling for this drug product does not include any indication or use covered by this patent.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Tramadol Hydrochloride Tablets, 50 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Ultram Tablets, 50 mg, of the R.W. Johnson Pharmaceutical Research Institute). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Validation of the regulatory methods has not been completed. It is the policy of the Office not to withhold approval until the validation is complete. We acknowledge your commitment to satisfactorily resolve any deficiencies that may be identified.

Sincerely yours,

Gary Buehler 6/24/02
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc: ANDA 75-962
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205
Endorsements:
HFD-649/ERamos/6/24/02
HFD-649/GJSmith/6/24/02
HFD-617/J.Min/6/24/02
HFD-613/C.Park/6/19/02
HFD-613/L.Golson/6/19/02

Robert Lewis 6/24/2002

V:\FIRMSNZ\WATSON\LTRS&REV\75962.AP.doc
F/T by: rlw/6/24/02

APPROVAL/ PACT

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-962

APPROVABLE LETTER

ANDA 75-962

JAN 15 2002

Watson Laboratories, Inc.
Attention: Ernest Lengle
311 Bonnie Circle
Corona, CA 92880

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated September 1, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act) for Tramadol Hydrochloride Tablets, 50 mg.

Reference is made to your amendments dated December 4, 2000; and April 23, June 1, and July 18, 2001.

We have completed the review of this ANDA as submitted, and have concluded that the application is **approvable.** However, before the application may receive final approval, issues involving the approved labeling for the reference listed drug product, Ultram® Tablets of R.W. Johnson Pharmaceutical Research Institute, and related exclusivity as described in 21 CFR 314.108(b)(5) will require resolution. The agency expects to complete its review of these issues as promptly as possible and you will be advised of the outcome. There is no additional material that you should submit to FDA at this time to obtain approval of your ANDA. The agency's recommendations will be provided to all ANDA applicants for this product at the appropriate time.

Any significant changes in the conditions outlined in your abbreviated new drug application as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (CGMPs) are subject to agency review before final approval of the application will be made.

This is not an approval letter. This drug product may not be marketed without final agency approval under Section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under Section 301(d) of the Act.

Also, until the agency issues the final approval letter, this drug product will not be deemed approved for marketing under Section 505 of the Act and will not be listed in "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"), published by the agency.

A copy of the recently approved package insert for Ultram® Tablets is available on the FDA Website at http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html. Please contact Robert L. West or Peter Rickman at (301) 827-5846 if you have further questions about this issue.

Sincerely yours,

Gary Buehler 1/15/02
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-962
Division File
Field Copy
GCF-1 Liz Dickinson
GCF-1 Kim Dettelbach
HFD-610/R.West
HFD-92
HFD-330
HFD-205/F.O.I.
HFD-92

Endorsements:
HFD-645/E.Ramos/ For Mahnaz Farahani 12,21,01
HFD-647/G.Smith/Mayra Pineiro for 9/11/01 12/21/01
HFD-617/J.Min/8/24/01 12/21/01
HFD-613/C.Park/12/19/01 12/21/01
HFD-613/C.Hoppes/ 12/21/01 12/22/2001

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F/t by rad12/20/01

APPROVABLE

comc satisfactory.
12/26/01.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-962

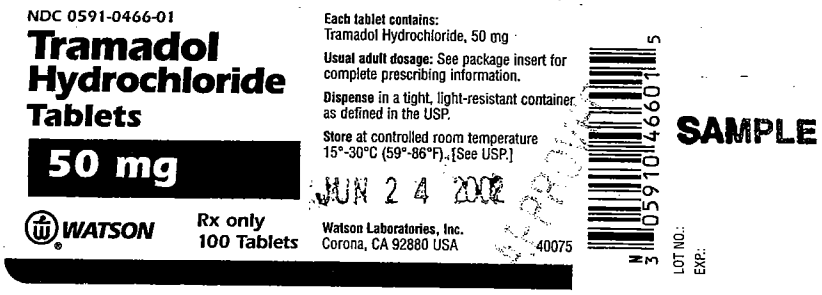
LABELING

Original

Container Labeling

Tramadol Hydrochloride Tablets, 50 mg

100 Tablets



Original

Container Labeling
Tramadol Hydrochloride Tablets, 50 mg
500 Tablets

NDC 0591-0466-05

Tramadol Hydrochloride Tablets

50 mg

WATSON

Rx only
500 Tablets

Each tablet contains:
Tramadol Hydrochloride, 50 mg

Usual adult dosage: See package insert for complete prescribing information.

Dispense in a tight, light-resistant container as defined in the USP.

Store at controlled room temperature 15°-30°C (59°-86°F). [See USP.]

JUN 2 4 2002 APPROVED

Watson Laboratories, Inc.
Corona, CA 92880 USA

40076

3 05910 46605 3

SAMPLE

LOT NO.:
EXP.:

Container Labeling
Tramadol Hydrochloride Tablets, 50 mg
1000 Tablets

NDC 0591-0466-10

Tramadol Hydrochloride Tablets

50 mg

WATSON

Rx only
1000 Tablets

Each tablet contains:
Tramadol Hydrochloride, 50 mg

Usual adult dosage: See package insert for complete prescribing information.

Dispense in a tight, light-resistant container as defined in the USP.

Store at controlled room temperature 15°-30°C (59°-86°F). [See USP.]

JUN 2 4 2002

APPROVED

Watson Laboratories, Inc.
Corona, CA 92880 USA

40077

SAMPLE

LOT NO.:
EXP.:

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-962

LABELING REVIEWS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-962 Date of Submission: September 1, 2000

Applicant's Name: Watson Laboratories, Inc.

Established Name: Tramadol Hydrochloride Tablets, 50 mg

Labeling Deficiencies:

1. GENERAL COMMENTS

   a. We acknowledge that you have not included the titration information approved on August 21, 1998 and December 23, 1999 for the insert labeling of the reference listed drug, Ultram®. We have reviewed the labeling submitted and have the following comments.

      Pending resolution of issues regarding the differences between your proposed dosing information of this drug product and that information in the last approved for the reference listed drug, Ultram®, we defer comment at this time.

   b. Revise the storage temperature statement to read "Store at controlled room temperature, 15° to 30°C (59° to 86°F) [see USP]".

2. CONTAINER – 100s, 500s, & 1000s

   a. Revise the established name to read "tramadol hydrochloride tablets".

   b. Revise to read:

      ...contains: Tramadol hydrochloride.....50 mg

   c. Refer to the general comment (b) above.

3. INSERT

   a. GENERAL

      i. Refer to the general comments above.

      ii. It is preferable to use the term "mcg" rather than "µg" throughout the text.

   b. DESCRIPTION

      Please identify the ingredients contained in your coating material, ———White ——— so that we can verify the listing of inactive ingredients.

   c. CLINICAL PHARMACOLOGY

      i. See general comment (a) above.

ii. Clinical Studies – Last paragraph, last sentence:

We encourage that you include a disclaimer identifying two brand names, "TYLENOL® with Codeine #3" and "TYLOX®". [e.g., Tylox® is the registered trade mark of Johnson RW]

d. INDICATIONS AND USAGE

... hydrochloride tablets are indicated... [add "tablets"]

e. PRECAUTIONS (Increased ... Trauma) – Last sentence:

... receiving tramadol hydrochloride tablets.

f. ADVERSE REACTIONS - First paragraph, last sentence:

See comment (c) above.

g. DOSAGE AND ADMINISTRATION

See general comment (a) above.

h. HOW SUPPLIED

i. Please note that the innovator has changed the scoring configuration from "unscored" to "scored" for Ultram® tablets. Please change the scoring configuration of your drug product to be same as the innovator's and revise this section accordingly.

ii. Refer to the general comment (b) above.

We will not request final printed insert labeling until we are able to provide adequate guidance regarding the differences of dosing information between your proposed labeling and that of the reference listed drug.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-
http://www.fda.gov/cder/ogd/rld/labeling review branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

William Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

NOTES/QUESTIONS TO THE CHEMIST:

i. We asked the sponsor to change the scoring figuration from "unscored" to "scored" to be the same as the innovator. Please follow up on this revision in terms of chemistry requirement. Please refer to OGD MaPP on this subject.

2. Please see comment 3(b) regarding inactive ingredients.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		x	
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?			
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	x		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the		x	

package insert accompany the product?			
Are there any other safety concerns?		x	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?			x
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		x	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		x	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			x
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD? (see FTR)	x		
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		x	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		x	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			x
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			x

USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		x	
Does USP have labeling recommendations? If any, does ANDA meet them?			x
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		x	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		x	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	x		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		x	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	x		

FOR THE RECORD:

1. MODEL LABELING – Ultram® Tablets (NDA 20-281/S-014 & 016, approved on August 21, 1998 and December 23, 1999, respectively)

2. This drug product is not the subject of a USP monograph.

3. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 90-E, B.1.1.

4. Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
020281	**002**	**D-44**	**AUG 21,2001**
020281	**002**	**NCE**	**MAR 03,2000**
020281	**002**	**PED**	**SEP 03,2000**
020281	**002**	**PED**	**FEB 21,2002**

D-44 (most likely tied with the pediatric exclusivity expires on 2/21/2002) was granted for the new titration information approved in S-014 on August 21, 1998. Another new titration information, which supersedes the subject of D-44, was approved on December 23, 1999 in S-016. At this time, the decision has not been made whether another exclusivity would be granted for this new titration information approved on December 23, 1999. The firm has carved out all titration information in order to market their product prior to the expiration of the exclusivity.

5. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

   Both RLD and the ANDA: Store at controlled room temperature (up to 25°C, 77°F). See general comment (b).

6. DISPENSING STATEMENT

RLD – Dispense in a tight container.

ANDA - Dispense in a tight container as defined in the USP.

7. PACKAGING CONFIGURATIONS

RLD: 100s, 500s & unit-doses of 100
ANDA – 100s, 500s, & 1000s

8. The tablets have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. See Vol.B.1.2, P.591

9. SCORING

The RLD is scored for both 50 mg & 100 mg strengths. ✓
The ANDA proposes unscored for 50 mg tablet.

The scoring of RLD has been changed from "unscored" to "scored" in association with the new titration information (starting with 25 mg) approved in S-016.

10. It has been determined between Charlie, Chan & Peter that the scoring of generic drug products should be the same as the innovators (i.e., scored) regardless whether the generic labeling should be allowed for the carving out of the titration information or not in accordance with OGD MaPP.

11. CLOSURE

Container – HDPE
Closure – 100s, 500s & 1000s (Non-CRC) [see p.461-462, B1.2]

12. Watson Laboratories, Inc. is the manufacturer of this product. (p.229, B.1.1)

Date of Review: 11/28/00 **Date of Submission: September 1, 2000**

Primary Reviewer: Chan Park Chan Park **Date:** 12/1/00

Team Leader: **Date:**

Charlie Hoppes 12/1/00

cc:

ANDA: 75-962
DUP/DIVISION FILE
HFD-613/CPark/CHoppes (no cc)
V:\FIRMSNZ\WATSON\LTRS&REV\75962na1.LABELING
Review

2.1 Veritas, S

(This review supersedes the one prepared on 11/28/01)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-962 Date of Submission: September 1, 2000

Applicant's Name: Watson Laboratories, Inc.

Established Name: Tramadol Hydrochloride Tablets, 50 mg

Labeling Deficiencies:

1. GENERAL COMMENTS

   a. Please note that a dosing exclusivity (D-63) was granted for the new titration information approved on December 23, 1999, for the insert labeling of the reference listed drug, Ultram®. Please update your Exclusivity Statements accordingly.

   b. We acknowledge that you have not included the titration information approved on August 21, 1998 and December 23, 1999 for the insert labeling of the reference listed drug, Ultram®. We have reviewed the labeling submitted and have the following comments.

      Pending resolution of issues regarding the differences between your proposed dosing information of this drug product and that information in the last approved for the reference listed drug, Ultram®, we defer comment at this time.

   c. Revise the storage temperature statement to read "Store at controlled room temperature, 15° to 30°C (59° to 86°F) [see USP]".

2. CONTAINER – 100s, 500s, & 1000s

   a. Revise the established name to read "tramadol hydrochloride tablets".

   b. Revise to read:

      ...contains: Tramadol hydrochloride.....50 mg

   c. Refer to the general comment (b) above.

3. INSERT

   a. GENERAL

      i. Refer to the general comments above.

      ii. It is preferable to use the term "mcg" rather than "µg" throughout the text.

   b. DESCRIPTION

      Please identify the ingredients contained in your coating material, ——— White ——— so that we can verify the listing of inactive ingredients.

c. CLINICAL PHARMACOLOGY

i. See general comment (a) above.

ii. Clinical Studies – Last paragraph, last sentence:

We encourage that you include a disclaimer identifying two brand names, "TYLENOL® with Codeine #3" and "TYLOX®". [e.g., Tylox® is the registered trade mark of Johnson RW]

d. INDICATIONS AND USAGE

... hydrochloride tablets are indicated... [add "tablets"]

e. PRECAUTIONS (Increased ... Trauma) – Last sentence:

... receiving tramadol hydrochloride tablets.

f. ADVERSE REACTIONS - First paragraph, last sentence:

See comment (c) above.

g. DOSAGE AND ADMINISTRATION

See general comment (a) above.

h. HOW SUPPLIED

i. Please note that the innovator has changed the scoring configuration from "unscored" to "scored" for Ultram® tablets. Please change the scoring configuration of your drug product to be same as the innovator's and revise this section accordingly.

ii. Refer to the general comment (b) above.

We will not request final printed insert labeling until we are able to provide adequate guidance regarding the differences of dosing information between your proposed labeling and that of the reference listed drug.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-
http://www.fda.gov/cder/ogd/rld/labeling review branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

William Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

NOTES/QUESTIONS TO THE CHEMIST:

i. **We asked the sponsor to change the scoring figuration from "unscored" to "scored" to be the same as the innovator. Please follow up on this revision in terms of chemistry requirement. Please refer to OGD MaPP on this subject.**

2. **Please see comment 3(b) regarding inactive ingredients.** Included 4/23/01 ps,

---

FOR THE RECORD:

1. MODEL LABELING – Ultram® Tablets (NDA 20-281/S-014 & 016, approved on August 21, 1998 and December 23, 1999, respectively)

2. This drug product is not the subject of a USP monograph.

3. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 90-E, B.1.1.

4. Patent Data

There are no unexpired patents for this product in the Orange Book Database.

[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]

Exclusivity Data

020281	002	D-63	DEC 23,2002
020281	002	D-44	AUG 21,2001
020281	002	NCE	MAR 03,2000
020281	002	PED	SEP 03,2000
020281	002	PED	FEB 21,2002

D-44 (tied with the pediatric exclusivity expires on 2/21/2002) was granted for the new titration information approved in S-014 on August 21, 1998. Another new titration information, which supersedes the subject of D-44, was approved on December 23, 1999 in S-016. Another exclusivity D-63 was granted for this new titration information.

5. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

   Both RLD and the ANDA: Store at controlled room temperature (up to 25°C, 77°F). See general comment (b).

6. DISPENSING STATEMENT

   RLD – Dispense in a tight container.

   ANDA - Dispense in a tight container as defined in the USP.

7. PACKAGING CONFIGURATIONS

   RLD: 100s, 500s & unit-doses of 100
   ANDA – 100s, 500s, & 1000s

8. The tablets have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. See Vol.B.1.2, P.591

9. SCORING

The RLD is scored for both 50 mg & 100 mg strengths.
The ANDA proposes unscored for 50 mg tablet.

The scoring of RLD has been changed from "unscored" to "scored" in association with the new titration information (starting with 25 mg) approved in S-016.

10. It has been determined between Charlie, Chan & Peter that the scoring of generic drug products should be the same as the innovators (i.e., scored) regardless whether the generic labeling should be allowed for the carving out of the titration information or not in accordance with OGD MaPP.

11. CLOSURE

Container – HDPE
Closure – 100s, 500s & 1000s (Non-CRC) [see p.461-462, B1.2]

12. Watson Laboratories, Inc. is the manufacturer of this product. (p.229, B.1.1)

13. ADVERSE REACTIONS

The following is the e-mail sent to PM in the new drug division regarding an adverse reaction "SKIN: Pruritis". We are awaiting the answer and will ask the firm a revision on this if necessary after receiving the answer.

Hi Yoon,

We note that the last item under ADVERSE REACTIONS "Skin: Pruritis" appearing in the insert labeling approved on August 21, 1998 (S-014) is NOT found in the labeling approved on December 23, 1999 (S-016). There is no reference to this change in the approval letter of S-016. Could it be an inadvertent omission ? Please let me know. Thank you,

---

Date of Review: 2/21/01 **Date of Submission: September 1, 2000**

Primary Reviewer: Chan Park **Date:** 2/22/01

Team Leader: **Date:** 2/22/01

cc:

ANDA: 75-962
DUP/DIVISION FILE
HFD-613/CPark/CHoppes (no cc)
V:\FIRMSNZ\WATSON\LTRS&REV\75962na1A.LABELING
Review

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-962 Date of Submission: April 23, 2001 & July 18, 01

Applicant's Name: Watson Laboratories, Inc.

Established Name: Tramadol Hydrochloride Tablets, 50 mg

Labeling Deficiencies:

INSERT

1. General

   a. Please revise your insert labeling to be in accordance with new labeling changes in the attached insert labeling for Ultram®, which was approved on August 15, 2001.

   b. We acknowledge that you do not seek approval of labeling that includes the new dosing schedule protected by the D-44 and D-63 exclusivities. We have reviewed the labeling submitted and have the following comments.

      Pending resolution of issues regarding the differences between your proposed dosing information of this drug product and that information in the last approved for the reference listed drug, Ultram®, we defer comment at this time.

2. Clinical Pharmacology - Figure 1

   It appears that the legends in this figure do not accurately represent the graph. Please revise the legends or graph so that they match each other.

3. How Supplied

   We encourage that you retain the NDC numbers.

We will not request final printed insert labeling until we are able to provide adequate guidance regarding the differences of dosing information between your proposed labeling and that of the reference listed drug.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-
http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

William Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachment: A copy of the last approved labeling for Ultram®.

FOR THE RECORD:

1. MODEL LABELING – Ultram® Tablets (NDA 20-281/S-029, approved on August 15, 2001). New labeling changes for S-029 are to strengthen WARNINGS and PRECAUTIONS sections, which is not associated with exclusivity.

2. This drug product is not the subject of a USP monograph.

3. Container labels are satisfactory in FPL as of 4/23/01 submission.

4. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 90-E, B.1.1. See also Exibit 1 of the 4/23/01 submission regarding the inactive ingredients contained in the coating material.

5. Patent Data

There are no unexpired patents for this product in the Orange Book Database.

[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
020281	002	PED	FEB 21,2002
020281	002	PED	JUN 23,2003
020281	002	D-63	DEC 23,2002
020281	002	D-44	AUG 21,2001

D-44 (tied with the pediatric exclusivity expires on 2/21/2002) was granted for the new titration information approved in S-014 on August 21, 1998. Another new titration information, which supersedes the subject of D-44, was approved on December 23, 1999 in S-016. Another exclusivity D-63 was granted for this new titration information.

The sponsor's update Exclusivity statement is accurate.

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

RLD : Store at controlled room temperature (up to 25°C, 77°F).
ANDA: Store at controlled room temperature, 15 to 30°C (59 to 86°F). [see USP]

DISPENSING STATEMENT

RLD – Dispense in a tight container.

ANDA - Dispense in a tight container as defined in the USP.

7. PACKAGING CONFIGURATIONS

RLD: 100s, 500s & unit-doses of 100
ANDA – 100s, 500s, & 1000s

8. The tablets have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. See Vol.B.1.2, P.591. The sponsor has changed the tablet code numbers on the tablet from —— to "446". The related chemistry information has been submitted for review in the submission of 4/23/01.

9. SCORING

The RLD is scored for both 50 mg & 100 mg strengths.
The ANDA is scored.

The scoring of RLD has been changed from "unscored" to "scored" in association with the new titration information (starting with 25 mg) approved in S-016. We have to resolve this scoring issue in conjunction with the exclusivity issue.

10. It has been determined between Charlie, Chan & Peter that the scoring of generic drug products should be the same as the innovators (i.e., scored) regardless whether the generic labeling should be allowed for the carving out of the titration information or not in accordance with OGD MaPP.

11. CLOSURE

Container – HDPE
Closure – 100s, 500s & 1000s (Non-CRC) [see p.461-462, B1.2]

12. Watson Laboratories, Inc. is the manufacturer of this product. (p.229, B.1.1)

13. It has been determined between OGD and the new drug division that the generic labeling should contain the first titration information approved August, 1998. However, we determined that generic does not have to wait for the expiration of the exclusivity granted for the new titration information approved December, 1999, which means that the generic labeling would not have to contain the second titration information for an approval. Therefore, OGD will allow the generic sponsors use the discontinued RLD labeling (without the second titration information). GC is working with the new drug division to develop a guidance regarding this issue to provide a legal basis for going back to the discontinued RLD labeling. New labeling changes for S-029 are to strengthen WARNINGS and PRECAUSTIONS SECTIONS, which is not associated with exclusivity.

Date of Review: 8/28/01 **Date of Submission: 4/23/01**

Primary Reviewer: Chan Park **Date:** 8/29/01

Team Leader: **Date:** 8/29/01

cc:

ANDA: 75-962
DUP/DIVISION FILE
HFD-613/CPark/CHoppes (no cc)
V:\FIRMSNZ\WATSON\LTRS&REV\75962na2.LABELING.doc

Review

(APPROVAL SUMMARY)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-962 Date of Submission: June 13, 2002

Applicant's Name: Watson Laboratories, Inc.

Established Name: Tramadol Hydrochloride Tablets, 50 mg

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

CONTAINER LABELS: 100s, 500s, & 1000s

Satisfactory in FPL as of 6/13/02 submission (vol. 3.1, 100s - #40075; 500s - #40076; 1000s - #40077)

PROFESSIONAL PACKAGE INSERT LABELING:

Satisfactory in FPL as of 6/13/02 submission (Issued May 2002, Code# 30354-1, vol. 3.1)

REVISIONS NEEDED POST-APPROVAL - INSERT:

1. GENERAL

   Increase the prominence, the figures in particular.

2. HOW SUPPLIED

   The issue date should be "June 02" rather than "May 2002".

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Ultram® Tablets

NDA Number: 20-281

NDA Drug Name: Ultram® Tablets

NDA Firm: R.W, Johnson

Date of Approval of NDA Insert and supplement #: August 15, 2001/S-029

Has this been verified by the MIS system for the NDA?
Yes

Was this approval based upon an OGD labeling guidance? **Yes**

Based on the OGD labeling proposal sent to the sponsor on June 11, 2001 via e-mail attachment.

If yes, give date of labeling guidance: June 11, 2002

FOR THE RECORD:

1. MODEL LABELING – Ultram® Tablets (NDA 20-281/S-029, approved on August 15, 2001).

   However, this labeling was modified due to the exclusivity and patent issue associated with 16-day titration information. The OGD proposal for the sponsors was based on the numerous consults with the HFD-550 and G.C. OGD carved out the information specific to the 16-day titration and also made some editorial changes in the D&A section.

2. This drug product is not the subject of a USP monograph.

3. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 90-E, B.1.1. See also Exibit 1 of the 4/23/01 submission regarding the inactive ingredients contained in the coating material.

4. Patent Data

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Use Code
020281	002	6339105	OCT 12,2019	U-435
020281	002	6339105*PED	APR 12,2020	U-435

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
020281	002	PED	FEB 21,2002
020281	002	PED	JUN 23,2003
020281	002	D-63	DEC 23,2002

6,339,105 - Analgesic regimen

D-63 - TO ALLOW A TITRATION DOSING REGIMEN USING A 25MG DOSE

U-435 A TITRATION DOSING REGIMEN FOR THE TREATMENT OF PAIN USING AN INITIAL DOSE OF ABOUT 25MG

5. The sponsor's updated Patent and Exclusivity statement submitted June 13, 2002 (signed June 11, 2002) is accurate.

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

   RLD : Store at controlled room temperature (up to 25°C, 77°F).
   ANDA: Store at controlled room temperature, 15 to 30°C (59 to 86°F). [see USP]

   DISPENSING STATEMENT

   RLD – Dispense in a tight container.

   ANDA - Dispense in a tight container as defined in the USP.