

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-782

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

1.3.5.1 Patent Information

Reference is made to the subject NDA 21-782 for Σ η (ramelteon) tablets for the treatment of insomnia and the requirements of 505 (b)(1) of the Federal Food, Drug and Cosmetic Act as amended and 21 CFR 314.501(c)(2).

Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act requires that "The applicant shall file with the (new drug) application the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use or sale of the drug"

The following patents were issued for TAK-375. The drug product name for this chemical entity is Σ η

21 CFR 314.53 (c) (i), (ii), (iii), (iv)

US Patent No.	Expiration Date	Type of Patent	Patent Owner	US Representative
6,034,239	March 7, 2017	Drug substance, Compound	Takeda Pharmaceutical Company, Ltd. (TCI)	Takeda Global Research and Development Center, Inc.

Appears This Way
On Original

1.3.5.2 Patent Certification

Reference is made to the subject NDA 21-782 for $\text{C}_{17}\text{H}_{19}\text{N}$ (ramelteon) tablets for the treatment of insomnia and the requirements of 505 (b)(1) of the Federal Food, Drug and Cosmetic Act as amended and 21 CFR 314.501(c)(2).

Declaration under 21 CFR 314.53(c)(2)

The applicant declares that Patent No, 6,034,239 covers the drug substance, compound.

This product is the subject of this application for which approval is sought.

As provided for under the Patent Term Restoration Act, Takeda Global Research & Development Center, Inc. will be requesting patent term restoration upon receipt of approval of $\text{C}_{17}\text{H}_{19}\text{N}$ (ramelteon).

Appears This Way
On Original

1.3.5.1 Patent Information

Reference is made to the subject NDA 21-782 for [redacted] (ramelteon) tablets for the treatment of insomnia and the requirements of 505 (b)(1) of the Federal Food, Drug and Cosmetic Act as amended and 21 CFR 314.501(c)(2).

Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act requires that "The applicant shall file with the (new drug) application the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use or sale of the drug"

The following patents were issued for TAK-375. The drug product name for this chemical entity is [redacted]

21 CFR 314.53 (c) (i), (ii), (iii), (iv)

US Patent No.	Expiration Date	Type of Patent	Patent Owner	US Representative
6,034,239	March 7, 2017	Drug substance, Compound	Takeda Pharmaceutical Company, Ltd. (TCL)	Takeda Global Research and Development Center, Inc.

Appears This Way
On Original

1.3.5.2 Patent Certification

Reference is made to the subject NDA 21-782 for [] (ramelteon) tablets for the treatment of insomnia and the requirements of 505 (b)(1) of the Federal Food, Drug and Cosmetic Act as amended and 21 CFR 314.501(c)(2).

Declaration under 21 CFR 314.53(c)(2)

The applicant declares that Patent No, 6,034,239 covers the drug substance, compound.

This product is the subject of this application for which approval is sought.

As provided for under the Patent Term Restoration Act, Takeda Global Research & Development Center, Inc. will be requesting patent term restoration upon receipt of approval of [] (ramelteon).

Appears This Way
On Original

EXCLUSIVITY SUMMARY

NDA # 21-782

SUPPL # ---

HFD # 170

Trade Name: Rozerem Tablets 8 mg

Generic Name: ramelteon

Applicant Name: Takeda Global Research & Development Center, Inc

Approval Date, If Known: July 22, 2005

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

n/a

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

n/a

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Requested Market Exclusivity determination. Did not specify a timeframe.

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

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

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

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

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

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

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

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a

Explain:

! Explain:

Investigation #2

!

YES

! NO

Explain:

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

Name of person completing form: Sara Stradley

Title: Regulatory Project Manager

Date: July 18, 2005

Concurred: Parinda Jani 7-18-05

Bob Rappaport 7-20-05

Copy sent to Lee Ripper 7-18-05

Name of Office/Division Director signing form: Robert J. Meyer

Title: Office Director, ODEII

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Robert Meyer
7/22/05 03:29:59 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-782 Supplement Type (e.g. SE5): N Supplement Number: 000

Stamp Date: 22 Sept 2004 Action Date: 22 July 2005

HFD 170 Trade and generic names/dosage form: ROZEREM (ramelteon) Tablets 8mg

Applicant: Takeda Global Research & Development Center Therapeutic Class: 2020400

Indication(s) previously approved: None

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: treatment of insomnia

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred: ALL

Min _____ kg _____ mo. _____ yr. 0 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 16 Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
 - Disease/condition does not exist in children
 - Too few children with disease to study
 - There are safety concerns with the use of this drug with known endocrine effects. More data needs to be accumulated in the adult population before its use in children.
 - Adult studies ready for approval
 - Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): July 22, 2012

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 21-782
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Sara Stradley
7/21/05 08:54:46 AM

Certification Statement
as requested by the
Generic Drug Enforcement Act of 1992

This certification statement is provided for New Drug Application (NDA) 21-782, drug code TAK-375 and is provided in compliance with the Generic Drug Enforcement Act of 1992.

I hereby certify that we did not and will not use in any capacity the services of any person debarred under subsection (a) or (b) of section 306 of the Federal Food, Drug and Cosmetic Act, (21 U.S.C. 335a (a) and (b)), were not used in any capacity in connection with this application.



October 1, 2004
Date



Certification Statement
as requested by the
Generic Drug Enforcement Act of 1992

This certification statement is provided for New Drug Application (NDA) 21-782, drug code TAK-375 and is provided in compliance with the Generic Drug Enforcement Act of 1992. Takeda Global Research & Development Center, Inc. hereby certifies that the applicant did not and will not use in any capacity the services of any person debarred under subsection (a) or (b) of section 306 of the Federal Food, Drug and Cosmetic Act, (21 U.S.C. 335a (a) and (b)), were not used in any capacity in connection with this application.



Stephen M. Sainati, M.D., Ph.D.
Vice President, Clinical Research
CNS, MPDRAP IIIb
Takeda Global Research & Development

9/29/04
Date

[]

[]

Certification Statement
as requested by the
Generic Drug Enforcement Act of 1992

This certification statement is provided for New Drug Application (NDA) 21-782, drug code TAK-375 and is provided in compliance with the Generic Drug Enforcement Act of 1992.

[] hereby certifies that we did not and will not use in any capacity the services of any person debarred under subsection (a) or (b) of section 306 of the Federal Food, Drug and Cosmetic Act, (21 U.S.C. 335a (a) and (b)), were not used in any capacity in connection with this application.

 /S/
[]

 01-10-04
Date

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-782	Efficacy Supplement Type SE-	Supplement Number
Drug: Rozerem (ramelteon)		Applicant: Takeda Global Research & Development Center
RPM: Sara Stradley		HFD-170 Phone # 301-827-7430
<p>Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p><input type="checkbox"/> Confirmed and/or corrected</p>		<p>Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s):</p> <p style="font-size: 1.2em; font-weight: bold;">NOTE: THIS Action package was recreated because the original package was misplaced and never made it to the CDR</p>
<p>❖ Application Classifications:</p> <ul style="list-style-type: none"> • Review priority • Chem class (NDAs only) • Other (e.g., orphan, OTC) 		<p><input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority</p> <p>IS</p>
<p>❖ User Fee Goal Dates</p>		July 22, 2005
<p>❖ Special programs (indicate all that apply)</p>		<p><input checked="" type="checkbox"/> None</p> <p><input type="checkbox"/> Subpart H</p> <p style="padding-left: 20px;"><input type="checkbox"/> 21 CFR 314.510 (accelerated approval)</p> <p style="padding-left: 20px;"><input type="checkbox"/> 21 CFR 314.520 (restricted distribution)</p> <p><input type="checkbox"/> Fast Track</p> <p><input type="checkbox"/> Rolling Review</p> <p><input type="checkbox"/> CMA Pilot 1</p> <p><input type="checkbox"/> CMA Pilot 2</p>
<p>❖ User Fee Information</p> <ul style="list-style-type: none"> • User Fee • User Fee waiver • User Fee exception 		<p><input checked="" type="checkbox"/> Paid UF ID number 4763</p> <p><input type="checkbox"/> Small business</p> <p><input type="checkbox"/> Public health</p> <p><input type="checkbox"/> Barrier-to-Innovation</p> <p><input type="checkbox"/> Other (specify)</p> <p><input type="checkbox"/> Orphan designation</p> <p><input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions)</p> <p><input type="checkbox"/> Other (specify)</p>
<p>❖ Application Integrity Policy (AIP)</p> <ul style="list-style-type: none"> • Applicant is on the AIP 		<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p>

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "No," continue with question (5)

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity)

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> Exclusivity summary Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	5 year exclusivity
<ul style="list-style-type: none"> Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. 	<input type="checkbox"/> Yes, Application # _____ <input checked="" type="checkbox"/> No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	7/21/05 (ADRA)

General Information	
<ul style="list-style-type: none"> ❖ Actions <ul style="list-style-type: none"> • Proposed action • Previous actions (specify type and date for each action taken) • Status of advertising (approvals only) 	<p>(x) AP () TA () AE () NA none (x) Materials requested in AP letter () Reviewed for Subpart H</p>
<ul style="list-style-type: none"> ❖ Public communications <ul style="list-style-type: none"> • Press Office notified of action (approval only) • Indicate what types (if any) of information dissemination are anticipated 	<p>(x) Yes () Not applicable (x) None () Press Release () Talk Paper () Dear Health Care Professional Letter</p>
<ul style="list-style-type: none"> ❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)) <ul style="list-style-type: none"> • Division's proposed labeling (only if generated after latest applicant submission of labeling) • Most recent applicant-proposed labeling • Original applicant-proposed labeling • Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings) • Other relevant labeling (e.g., most recent 3 in class, class labeling) 	<p>x x x x</p>
<ul style="list-style-type: none"> ❖ Labels (immediate container & carton labels) <ul style="list-style-type: none"> • Division proposed (only if generated after latest applicant submission) • Applicant proposed • Reviews 	<p>x x</p>
<ul style="list-style-type: none"> ❖ Post-marketing commitments <ul style="list-style-type: none"> • Agency request for post-marketing commitments • Documentation of discussions and/or agreements relating to post-marketing commitments 	<p>n/a n/a</p>
<ul style="list-style-type: none"> ❖ Outgoing correspondence (i.e., letters, E-mails, faxes) 	<p>x</p>
<ul style="list-style-type: none"> ❖ Memoranda and Telecons 	<p>x</p>
<ul style="list-style-type: none"> ❖ Minutes of Meetings <ul style="list-style-type: none"> • EOP2 meeting (indicate date) • Pre-NDA meeting (indicate date) • Pre-Approval Safety Conference (indicate date; approvals only) • Other 	<p>X 1/17/2003 and 11/8/2001 X 12/15/2003 and 6/22/2004 7/11/2005</p>
<ul style="list-style-type: none"> ❖ Advisory Committee Meeting <ul style="list-style-type: none"> • Date of Meeting • 48-hour alert 	<p>n/a</p>
<ul style="list-style-type: none"> ❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable) 	<p>n/a</p>

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) <i>(indicate date for each review)</i>	7/22/05 (Office) 7/18/05 (Director) 7/22/05, 6/30/05 (MO TL)
Clinical Information	
❖ Clinical review(s) <i>(indicate date for each review)</i>	7/22/05, 6/29/05
❖ Microbiology (efficacy) review(s) <i>(indicate date for each review)</i>	n/a
❖ Safety Update review(s) <i>(indicate date or location if incorporated in another review)</i>	see clinical review
❖ Risk Management Plan review(s) <i>(indicate date location if incorporated in another rev)</i>	See CSS review
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	X
❖ Demographic Worksheet <i>(NME approvals only)</i>	see clinical review
❖ Statistical review(s) <i>(indicate date for each review)</i>	6/22/05
❖ Biopharmaceutical review(s) <i>(indicate date for each review)</i>	6/30/05, 6/21/05
❖ Controlled Substance Staff review(s) and recommendation for scheduling <i>(indicate date for each review)</i>	6/13/05
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	6/13/05
• Bioequivalence studies	
CMC Information	
❖ CMC review(s) <i>(indicate date for each review)</i>	7/22/05 (ONDCH) 7/22/05, 6/29/05, 6/10/05
❖ Environmental Assessment	
• Categorical Exclusion <i>(indicate review date)</i>	See CMC review
• Review & FONSI <i>(indicate date of review)</i>	See CMC review
• Review & Environmental Impact Statement <i>(indicate date of each review)</i>	See CMC review
❖ Microbiology (validation of sterilization & product sterility) review(s) <i>(indicate date for each review)</i>	n/a
❖ Facilities inspection (provide EER report)	Date completed: (X) Acceptable () Withhold recommendation
❖ Methods validation	() Completed (X) Requested () Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	7/13/05 (Assoc Direct) 6/28/05 (supervisor) 6/22/05 (reviewer)
❖ Nonclinical inspection review summary	n/a
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	3/01/05
❖ CAC/ECAC report	3/25/05

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Sara Stradley
7/26/05 02:39:36 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

APR 9 2005

John Yates, M.D., President
Takeda Global Research and Development
475 Half Day Road
Lincolnshire, Illinois 60069-2934

Dear Dr. Yates:

Between April 19 and 27, 2005, Ms. Lisa Hayka, representing the Food and Drug Administration (FDA), conducted an inspection and met with you and other members of your firm to review your conduct as sponsor of 4 clinical investigations of the investigational drug Rozerem (ramelteon, TAK-375).

Protocol No.: 01-02-TL-375-017, A Phase III, Randomized, Double-Blind, Placebo-Controlled, Crossover Study to Determine the Safety and Efficacy of TAK-375 in Elderly Subjects with Chronic Insomnia

Protocol No.: 01-02-TL-375-021, A Phase III, Randomized, Double-Blind, Placebo-Controlled PSG plus Outpatient Study to Determine the Safety and Efficacy of TAK-375 in Adults with Chronic Insomnia

Protocol No.: 01-02-TL-375-023, A Phase III, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Single-Dose Study of TAK-375 in Healthy Volunteers in a Sleep Lab Model of Transient Insomnia

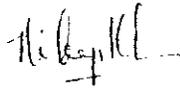
Protocol No.: 01-02-TL-375-025, A Phase III, Randomized, Double-Blind, Placebo-Controlled, Outpatient, Safety and Efficacy of TAK-375 in Elderly Subjects with Chronic Insomnia

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our evaluation of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Hayka during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,



Ni A. Khin, M.D.
Branch Chief
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

cc:

Claire M. Thom, PharmD, Senior Vice President
Quality Assurance, Due Diligence, and Compliance and Safety
Takeda Global Research and Development
475 Half Day Road
Lincolnshire, Illinois 60069-2934

CFN/FEI []

Field Classification: NAI

Headquarters Classification:

1) NAI

2) VAI- no response required

3) VAI- response requested

4) OAI

cc:

HFA-224

HFD-170 Doc.Rm. NDA#21-782

HFD-170 Review Div.Dir. (Rappaport)

HFD-170 MO (McNeil)

HFD-170 PM (Stradley)

HFD-46/47c/r/s/ GCP File #11538

HFD-46/47 GCP Reviewer (Currier)

HFD-47 Branch Chief (Khin)

HFD-46/47 CS

HFR-CE650 DIB (Berg)

HFR-CE652 Bimo Monitor (Yuscus)

HFR-CE650 Field Investigator (Hayka)

GCF-1 Seth Ray

r/d:cac:8/4/05

reviewed: NK:8/8/05

f/t: cac:8/9/05

o:\Takeda.SM.PDUFA [] (Rozerem).N21782.NAI.LTR.doc

Reviewer Note to Rev. Div. M.O.

The inspection of Takeda was issued on a routine basis; DSI routinely inspects sponsors submitting applications with new molecular entities. The inspection revealed that both sponsoring and monitoring procedures appeared adequate. No deviations from FDA regulations were noted and no 483 was issued to the firm.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Ni Aye Khin

8/24/2005 05:03:11 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research



OFFICE DIRECTOR'S DECISIONAL MEMORANDUM

Date: Friday, July 22, 2005
NDA: 21-782
Sponsor: Takeda Pharmaceuticals
Proprietary Name: Rozerem (ramelteon) 8 mg tablet
Author: Robert J. Meyer, MD, Director, ODE II

Summary: This is a very brief memorandum, as Dr. Rappaport's summary memo of July 18th represents a document with which I am in substantial accord and I refer readers to that memo as the memorandum of record for this action.

Takeda has presented adequate evidence of safety and efficacy for this product through a reasonably extensive clinical program, supporting the indication of aiding sleep onset in the setting of insomnia. They did not show substantial data for a [] claim and, curiously, they did not show much consistent subjective improvement even when objective measures by polysomnography did. Ultimately, since this is a medication taken for subjective reasons, patients will need to decide if they perceive a benefit and if that benefit outweighs any adverse effects they may feel. On the safety side, this drug was reasonably well tolerated, with some excess in somnolence and fatigue reported, along with a few other CNS effects (including aggravated insomnia), along with a small increase in nausea. As far as safety issues beyond tolerability, the drug did appear to lead to mildly elevated prolactin levels in some females, but there were no reported consequences of this elevation seen in the trials (i.e., amenorrhea, galactorrhea, etc.). One prolactinoma was seen in the trials, but timing would make this unlikely to be primarily due to drug. Dr. Mary Parks of DMEDP provided a very useful consult on the endocrine effects of this drug and this consult has led to appropriate labeling for checking prolactin levels in patients with symptoms/signs consistent with hyperprolactinemia.

As noted in Dr. Rappaport's memo, this drug is subject to a number of drug interactions (though itself, it is neither an apparent inhibitor or inducer of CYP enzymes). The most extreme interaction is with fluvoxamine (a strong CYP1A2 inhibitor) and for this one drug, we are warning against concomitant use, though no safety issues were identified in the small PK study done to examine this interaction. Most other CYP1A2 inhibitors (which are few known cases) are less strong and hence a caution will be urged for their concomitant use. The drug is also extensively metabolized in the liver and, therefore, it must be used with caution in patients with mild or moderate hepatic impairment and should not be used in those with severe hepatic disease.

One change to labeling worth noting in this brief memo was to the section on COPD and respiratory depression (since it emanated from the ODE review). The sponsor had wished, based

[that appropriately proposed [] the label they had]
] labeling now clearly states that no studies of patients with CO₂ retention or needing nocturnal oxygen were studied.

There are no phase 4 studies needed for this product, other than pediatric studies, but due to the effect of this melatonin-like drug on prolactin levels, we will need to be vigilant in our post-marketing assessments for any signs of important endocrine disruption which might signal more of an issue with this drug than we now perceive or that Dr. Parks expressed. Given this lingering question, it seems prudent to delay the requirement of pediatric data at least 5 years (and I favor seven) to allow time for marketing in adults and experience in a broader use setting prior to studying and approving this drug for adolescents or other children who might be particularly susceptible to disruptive endocrine effects, if indeed any exist.

In summary, as per Dr. Rappaport's memo, Takeda has provided adequate evidence to support the approval of ramelteon as a hypnotic for the treatment of sleep-onset issues.

**Appears This Way
On Original**

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Robert Meyer
7/22/05 12:39:46 PM
MEDICAL OFFICER



FDA CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ANESTHESIA, ANALGESIA AND RHEUMATOLOGY PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857

Tel:(301) 827-7410

DIVISION DIRECTOR SUMMARY REVIEW AND RECOMMENDATION FOR APPROVAL

DATE: July 18, 2005

DRUG: Rozerem (ramelteon, 8-mg tablets)

NDA: 21-782

NDA Code: Type 1S NDA

SPONSOR: Takeda Global Research & Development Center Inc.

INDICATION: For the treatment of insomnia

Takeda submitted NDA 21-782 in support of marketing approval for Rozerem, 8-mg tablets, on September 21, 2004.

Review of the CMC portion of this application was completed by Pramoda Maturu, Ph.D. Review of the general pharmacology and toxicology data presented in this application was completed by Adam M. Wasserman, Ph.D. Supervisory reviews were provided by Daniel Mellon, Ph.D., Supervisory Pharmacologist in this division and by Kenneth L. Hastings, Ph.D., Associate Director for Pharmacology and Toxicology, Office of Drug Evaluation II. Review of the clinical pharmacology and biopharmaceutics data in the application was completed by David Lee, Ph.D. A statistical review and evaluation was completed by Dionne Price, Ph.D. The clinical review was completed by D. Elizabeth McNeil, M.D. and a supervisory review of the clinical data was submitted by Rigoberto Roca, M.D., Deputy Director of this division. Consultation on this application was also obtained from the Division of Metabolic and Endocrine Drug Products, the Controlled Substance Staff (CSS), the Division of Drug Marketing, Advertising and Communications (DDMAC), and the Office of Drug Safety (ODS).

Ramelteon is a melatonin receptor agonist. It has high affinity for the MT₁ and MT₂-receptor subtypes, and little affinity for the MT₃-receptor subtype or other receptors types. Its active metabolite, M-II, has a similar binding profile. Binding at the MT₁ and MT₂-receptor subtypes by melatonin is thought to affect circadian rhythms, including the sleep-wake cycle. Specifically in regard to the sleep-wake cycle, melatonin is thought to induce sleep via damping of the continuous alerting stimulus that normally arises from the suprachiasmatic nucleus. This is the basis for the original preclinical investigation of ramelteon and for the introduction of a clinical development plan. Up to and through the end of Phase 2, the IND for this product was located in the Division of Neuropharmacological Drug Products (DNPD). The IND was transferred to this division in September of 2003.

Efficacy:

Reports for seven randomized controlled clinical trials were submitted with this application. These studies have been thoroughly reviewed by Drs. McNeil, Price and Roca. Therefore, I will only briefly summarize their findings.

Transient Insomnia Studies:

Study PNFP002 (002):

This study evaluated doses of 16 and 64 mg and will not be included in the efficacy evaluation of the product.

Study TL023 (023):

This was a randomized, double-blind, placebo-controlled, parallel-group trial which compared single doses of Rozerem 8 and 16 mg to placebo in healthy adult subjects. The patients were evaluated in sleep laboratories, receiving study drug or placebo 30 minutes before their usual sleep time. The primary outcome assessment was latency to persistent sleep (LPS) as measured by polysomnography (PSG). A statistically significant treatment effect (8 minutes) was demonstrated for the 8-mg dose of Rozerem compared to placebo, but not for the 16-mg dose. A categorical analysis (proportion of subjects with LPS less than or equal to 30 minutes) performed by the sponsor did not show a treatment effect for either dose.

Secondary efficacy measures included polysomnographically determined: total sleep time (TST), sleep efficiency (SE), awake time after persistent sleep, number of awakenings after persistent sleep and percentage of time in each sleep stage. Additional subjective measures included: time to sleep onset, total sleep time, restorative nature of sleep, awake time, number of awakenings, ease of falling back to sleep, and sleep quality. Only TST

and SE (measures influenced by sleep latency) showed statistically significant treatment effects. None of the subjective measures were supportive of the primary efficacy analysis.

Chronic Insomnia Studies with Objective Outcome Measures:

Study TL005 (005):

This was a randomized, double-blind, placebo-controlled, crossover, dose-response trial that compared 4, 8, 16 and 32 mg of Rozerem to placebo in otherwise healthy adult subjects with chronic insomnia. Each period lasted two days, with 5 to 12 days between periods. The primary outcome assessment was latency to persistent sleep (LPS) as measured by PSG on Nights 1 and 2 of each treatment period. A statistically significant treatment effect was demonstrated for each dose when compared to placebo. The differences in mean LPS scores ranged from 13 to 15 minutes and did not show a clear dose effect.

Secondary efficacy measures included polysomnographically determined: total sleep time (TST), sleep efficiency (SE), awake time after persistent sleep, and percentage of time in each sleep stage. Additional subjective measures included: time to sleep onset, total sleep time, and sleep quality. The objective measures were inconsistently supportive of the primary outcome assessment results. In regard to the subjective outcomes, a statistically significant result was only noted for the 16-mg group on the sleep latency measure.

Study TL017 (017):

This was a randomized, double-blind, placebo-controlled, crossover, dose-response trial that compared 4 and 8 mg of Rozerem to placebo in otherwise healthy subjects age 65 years and older with chronic insomnia. Each period lasted three days, with 5 to 12 days between periods. The primary outcome assessment was latency to persistent sleep as measured by PSG on Nights 1 and 2 of each dosing period. A statistically significant treatment effect was demonstrated for each dose when compared to placebo. The difference from placebo in mean LPS scores was 10 minutes for the 4-mg group and 8 minutes for the 8-mg group.

Secondary efficacy measures included polysomnographically determined: total sleep time (TST), sleep efficiency (SE), awake time after persistent sleep, number of awakenings after persistent sleep and percentage of time in each sleep stage. Additional subjective measures included: time to sleep onset, total sleep time, restorative nature of sleep, awake time, number of awakenings, ease of falling back to sleep, and sleep quality. Only TST and SE (measures influenced by sleep latency) showed statistically significant treatment effects for both dose groups. There was a statistically significant increase in the number of awakenings after sleep for the 4-mg group compared to placebo. In regard to the subjective outcomes, a statistically significant result was only noted for the 4-mg group on the sleep latency measure.

Study TL021 (021):

This was a randomized, double-blind, placebo-controlled, parallel-group trial that compared 8 and 16 mg of Rozerem to placebo in otherwise healthy subjects age 65 years and older with chronic insomnia. The primary outcome assessment was latency to persistent sleep as measured by PSG on two nights at Weeks 1, 3 and 5. Rebound insomnia and withdrawal were evaluated on a return visit on Nights 36 and 37. Patients were instructed to take study medication at home, nightly, between visits. There was a statistically significant treatment effect for each dose compared to placebo at each of the time periods. A categorical analysis (proportion of subjects with LPS less than or equal to 30 minutes) performed by the sponsor, and reanalyzed by Dr. Price, was mostly supportive of the primary outcome findings. No evidence of rebound insomnia or withdrawal was found.

Secondary efficacy measures included polysomnographically determined: total sleep time (TST), sleep efficiency (SE), awake time after persistent sleep, and number of awakenings after persistent sleep. Additional subjective measures included: time to sleep onset, total sleep time, awake time, number of awakenings, ease of falling back to sleep, and sleep quality. Statistically significant treatment effects for both doses were noted for SE and TST, but only at Week 1; although the 16-mg dose did show statistically significant treatment effects at Week 3. There were no statistically significant treatment effects for the 8-mg group on the subjective measures; although the 16-mg dose did show inconsistent support on these measures.

*Chronic Insomnia Studies with Subjective Outcome Measures:***Study TL020 (020):**

This was a randomized, double-blind, placebo-controlled, parallel-group outpatient trial that compared 8 and 16 mg of Rozerem to placebo in otherwise healthy adult subjects with chronic insomnia. The primary outcome assessment was mean subjective sleep latency over the initial seven nights of double-blind treatment. No treatment effect was demonstrated.

Study TL025 (025):

This was a randomized, double-blind, placebo-controlled, parallel-group outpatient trial that compared 4 and 8 mg of Rozerem to placebo in otherwise healthy subjects age 65 years and older with chronic insomnia. The primary outcome assessment was mean subjective sleep latency over the initial seven nights of double-blind treatment. There were statistically significant treatment effects for each dose compared to placebo (8 minutes for each dose), and the effect appeared to persist throughout Day 36 on secondary outcome analyses. A categorical analysis (proportion of subjects with LPS less than or equal to 30

minutes) performed by the sponsor did not show a treatment effect for either dose for Week 1.

No statistically significant treatment effects were found for other secondary outcome analyses such as subjective sleep quality, ease of falling back to sleep after awakening, number of awakenings, and Clinician's Clinical Global Impression. For subjective TST, a statistically significant treatment effect was only found for the 4-mg dose, and only for Weeks 1 and 3.

Clinical Safety:

A total of 3,594 subjects were exposed to Rozerem in the clinical development program. Dr. Roca's Exposure by Time table on page 7 of his review summarizes the actual data with regard to exposure, which for the doses that the sponsor proposes to recommend and market, is less than 180 for the bulk of the subjects.

Two deaths occurred in subjects exposed to Rozerem. Both subjects were killed when struck by automobiles; and the sponsor has concluded that these deaths were, therefore, unrelated to study drug. However, due to the soporific effects of Rozerem, and the not uncommon neuropsychiatric effects associated with the drug, some relation to these events cannot be completely ruled out. While one of these subjects left a diary indicating that her last dose of study drug was approximately 6 weeks prior to the accident, she was found to have a high blood ethanol level at autopsy, raising questions of substance abuse, drug-alcohol pharmacodynamic interactions, and reporter (patient) reliability.

In general, based on the adverse events noted in the clinical studies the overall safety profile of Rozerem was relatively benign. There were somewhat higher incidences of fatigue, myalgia, depression, eye pain and dyspepsia compared to placebo, but there was no dose effect for any of these adverse events. The serious adverse events and adverse events resulting in discontinuation in the Rozerem-treated subjects were similar to those that occurred in the placebo-treated subjects. There were no clinically significant differences in the adverse events reported by the younger adult and older adult subjects.

The only laboratory findings of clinical concern were related to the effects of Rozerem on the endocrinological system. Mary Parks, M.D., Deputy Director of the Division of Metabolic and Endocrine Drug Products, provided a detailed and thorough consultation on these findings. In her consult, she concludes that only the noted hyperprolactinemia was likely to be related to Rozerem exposure and to be clinically relevant. Dr. Parks notes that, while the degree of prolactin elevation was not in the range generally associated with prolactinomas, and there were no serious adverse events seen in association with the elevated levels, even mild, persistent hyperprolactinemia can result in dysregulation of the reproductive axis and consequent hypogonadism. Hypogonadism in turn may result in amenorrhea in women, and infertility and decreased libido in both sexes. Hypogonadism is also a risk factor for osteopenia and osteoporosis.

Therefore, Dr. Parks has recommended monitoring of prolactin levels in patients with clinical complaints or presentations of concern. She does not recommend routine monitoring as prolactin elevations can occur secondary to non-pathologic etiologies such as stress. Dr. Parks also recommends that, due to the fact that differences in prolactin levels were observed in only one placebo-controlled study with only 122 subjects randomized 1:1 for 6 months of treatment, monitoring in any future studies should be considered to obtain additional data on the extent and persistence of this laboratory abnormality.

In regard to the single case of prolactinoma in the Rozerem safety database, Dr. Parks notes the following in a follow-up personal communication:

I don't think we have sufficient evidence to say that ramelteon caused or even promoted the growth of an already-present prolactinoma. Prolactinomas are the most common functional pituitary tumors... Even if we conclude that ramelteon causes hyperprolactinemia I don't think that we can then conclude that it will induce tumor growth. Recall that many medications can cause prolactin elevations by disruption of dopamine secretion or direct stimulation of prolactin receptors but will have nothing to do with inducing pituitary adenomas.

Nonclinical Safety:

In his review, Dr. Wasserman reports on the following clinically important findings from the non-clinical studies:

- Due to the relatively, and significantly lower circulating levels of M-II in the animals studied during development, and to this metabolite's high level of activity, the exposure margins for both the parent compound and M-II should be included in the package insert.
- Due to the magnitude of the increase in hepatic adenomas, carcinomas and hepatoblastomas in male mice, and adenomas and carcinomas in female mice, compared to control-treated mice and historical control data, and the finding of clastinogenicity in one genetic toxicology study, this information should be included in the package insert.
- Due to the findings of a dose-dependent increased incidence of hepatic tumors in both male and female rats compared to control-treated rats and historical controls, and the finding of an increased incidence of Leydig cell tumors compared to control-treated rats and historical controls, these data should be included in the package insert.
- Although Rozerem exposure in rats was associated with teratogenicity, there is a large margin of safety (1,892-fold) based on pharmacokinetic data; and, although the safety margin is significantly less for the M-II metabolite (45-fold), appropriate discussion in the package insert should be adequate to address these findings.

In addition, Dr. Wasserman recommends:

- Full characterization of M-II in cardiovascular safety studies should be undertaken, as in vitro studies generally did not include this active metabolite and the submitted in vivo studies either would not be expected to evaluate M-II or did not assess the level of this metabolite.
- Full characterization of the inactive metabolite M-IV should be completed, in order to satisfy requirements for a non-rodent evaluation of toxicity.
- An in vitro chromosomal aberration assay in CHL or another system should be repeated to resolve methodological problems and to confirm or refute the positive clastogenic response observed in the original study.

However, in his supervisory review, Dr. Mellon concludes the following:

- Based on the sponsor's clinical QT study at doses of 32 and 64 mg of Rozerem, no further non-clinical cardiovascular safety studies should be necessary.
- As the rat toxicology studies provided a mean plasma concentration of M-IV at the NOAEL dose that establishes a margin of safety to support the NDA, and as the concentrations of M-IV at the monkey LOAEL provided acceptable coverage, even though the plasma concentrations of M-IV that produced no adverse effects in the monkey toxicology studies were below the mean plasma levels expected in humans at the maximum recommended daily dose (not an ideal characterization), he is able to conclude that acceptable support for the safety of the metabolite has been provided.
- As the sponsor did not provide a mechanistic explanation for the positive genotoxicity findings, they must be considered valid and cannot be dismissed. However, Dr. Mellon agreed with Dr. Wasserman's conclusion that the weight of evidence suggests an overall lack of genotoxic hazard, that further studies are not required, and that the existing data may be described in the labeling.

Clinical Pharmacology and Biopharmaceutics:

In his review, Dr. Lee reports the following clinically important findings regarding Rozerem:

- Rozerem appears to have a large inherent in vivo bioavailability, with an observed standard deviation as large as 100%.
- The active metabolite, M-II, is present in human serum in concentrations 20 to 100 times higher than the parent drug; but has approximately 1/10th and 1/5th the affinity of Rozerem for the MT₁ and MT₂ receptor subtypes, respectively.
- Sixty-four mg of Rozerem did not prolong the QT interval in a dedicated QT study.
- Rozerem's AUC_{0-∞} and C_{max} were 97% and 86% higher, respectively, and its T_{1/2} was 66% longer in older compared with younger subjects.

- M-II's $AUC_{0-\infty}$ and C_{max} were 30% and 13% higher, respectively, and its $T_{1/2}$ was 33% longer in older compared with younger subjects.
- Single- and multiple-dose exposure of 16 mg of Rozerem resulted in increases in AUCs of 3.5 to 3.6 fold and 8.0 to 10.7 fold in patients with mild and moderate hepatic impairment, respectively, compared to subjects with normal liver function. (Patients with severe hepatic impairment were not studied.)
- Administration of Rozerem with food results in a 30% increase in AUC, 22% decrease in C_{max} and one-hour increase in the $T_{1/2}$.

Dr. Lee, therefore, recommends:

- Rozerem should not be taken with food.
- Elderly patients should be prescribed one-half the usual adult dose, based on the pharmacokinetic data and the fact that all of the previously approved hypnotic drug products have been approved with recommendations for reduced dosing in the elderly.
- Rozerem should be contraindicated in patients with any degree of liver impairment.

In addition, Dr. Lee recommends that:

- Rozerem should be contraindicated for use with 1A2 inhibitors, as its AUC was increased 190-fold and its C_{max} increased 70-fold in an in vitro drug-drug interaction study with fluvoxamine.
- Rozerem should be used with caution with 2C9 inhibitors, as its AUC was increased by 52% and its C_{max} was increased by 44% in an in vitro drug-drug interaction study with fluconazole; and, the AUC and C_{max} of MII were increased by 200 and 55%, respectively in that study.
- Rozerem should be contraindicated for use with 3A4 inducers, as its AUC and C_{max} were both reduced by 80% in an in vitro drug-drug interaction study with rifampin; and, the AUC and C_{max} of MII were decreased by 89 and 81%, respectively in that study.

Finally, Dr. Lee notes that the pharmacokinetics of Rozerem have not been studied in smokers, and smoking induces CYP1A2 activity.

Chemistry, Manufacturing and Controls:

Dr. Maturu has concluded that there are no outstanding concerns regarding the chemistry, manufacturing or controls of Rozerem.

Nomenclature:

The sponsor's initial request for the trade name [redacted] was evaluated by the Division of Medication Errors and Technical Support (DMETS). The DMETS review team determined that Takeda should request a new trade name due the potential for confusion with the recently approved hypnotic Lunesta. Takeda requested Rozerem as an alternative and this trade name has been found to be acceptable.

Abuse Liability, Withdrawal Phenomena and Overdose:

In her consult, Katherine Bonson, Ph.D. has concluded that Rozerem does not have abuse liability similar to that of other scheduled products indicated for the treatment of insomnia. Further, no evidence of a withdrawal phenomenon was found in the clinical studies. There were no cases of overdose in the clinical database.

Discussion:

The sponsor has provided adequate evidence of the efficacy of Rozerem as a treatment for both transient and chronic sleep onset insomnia. They have not, however, provided any evidence that their product is effective as a treatment for [redacted] insomnia. In point of fact, they did not study outcome measures that would even allow for adequate assessment of a treatment effect in [redacted]. Thus the product may only be indicated for the treatment of sleep onset insomnia.

The results of the analyses of subjective improvement in sleep latency and quality of sleep were rather surprising. Only the patients in the outpatient, subjective-endpoint study in the elderly had clinically and statistically significant improvements in these measures. Below is the sponsor's hypothesis for why there was an absence of subjective improvement in the younger adults:

In contrast to objective measurements by PSG, subjective assessments of sleep may be influenced by other factors. Subjects with insomnia tend to overestimate sleep latency and underestimate sleep duration relative to PSG measurement...PSG changes can be measured even before the subject perceives sleepiness Subjects who are experienced with the use of benzodiazepines, in particular, may anticipate cues such as sedation and equate these sensations with falling asleep...Subjects treated with BZRAs may also underestimate sleep latency due to amnesic effects, forgetting how long they remained awake before falling asleep. This is analogous to preoperative use of benzodiazepines, which may produce anterograde amnesia...Given that the subjective assessment techniques in these studies were originally developed for compounds with GABAergic mechanisms of action, the absence of subjective anxiolytic, sedative, and muscle-relaxant effects prior to sleep onset may make the sleep-promoting effects of ramelteon more difficult to detect subjectively.

[Application Summary: Section 2.5; Part 4.0; Overview of Efficacy]

While this is a most interesting hypothesis and may well be the explanation for the unusual results, it is only a hypothesis. Nevertheless, I think that, as there is some evidence of subjective improvement in the older adults, and considering the relatively benign safety profile of Rozerem, it is reasonable to allow marketing of the product. Patients who are dissatisfied with the efficacy of the product will simply discontinue taking the medication.

The product's potential for causing hyperprolactinemia, and resultant hypogonadism, amenorrhea, infertility, decreased libido, osteopenia and osteoporosis, is of some concern. However, as Dr. Parks has concluded, patients presenting with symptoms or signs suggestive of this abnormality can be tested, and the drug discontinued. Therefore, it is unlikely that there will be significant residual morbidity. I do not think that post-marketing studies to evaluate the persistence and extent of hyperprolactinemia and the incidence of neoplasia, as recommended by Dr. McNeil, are necessary. However, I do recognize and agree with her concern regarding this effect, and, as such, it will be important to closely watch for any signals of more significant morbidity in the post-marketing period. Both the sponsor and the Division (working closely with the Office of Drug Safety), should regularly monitor the post-marketing reports for any of these abnormalities in the initial five years after approval, and continue observation over the long term to rule out any significant increases in osteoporosis in patients treated chronically with Rozerem. It should be noted that chronic treatment will be an off-label use of this product.

I do not agree with Dr. Roca's assessment that the sponsor has not provided evidence of clinical significance in their studies. While the mean differences in latency to sleep onset were small, this is not unusual for analyses that compare the means of different treatment groups. Indeed, review of the raw data demonstrates a wide range of outcomes, many of indisputable clinical relevance.

I agree with Dr. Mellon's conclusions and recommendations that further studies, as recommended by Drs. Wasserman and McNeil, are not necessary to assess the genotoxicity, carcinogenicity or reproductive toxicity of Rozerem. Nor do I think that the pregnancy registry recommended by Dr. McNeil is warranted, based on the large margin of safety found for the teratogenic effects of the drug.

I agree with Dr. Lee's recommendation that Rozerem should be contraindicated for use with CYP1A2 inhibitors due to the extremely large increases in the C_{max} and AUC of Rozerem when it was studied with fluvoxamine. I also agree that caution is warranted when it is administered with CYP2C9 inhibitors, and that practitioners should be alerted to the fact that there could be a decrease in or loss of efficacy when it is administered with CYP3A4 inducers; although I do not agree that is necessary to contraindicate co-administration of CYP3A4 inducers, as lack of efficacy should simply result in discontinuation of treatment. Nor do I agree with Dr. Lee that is necessary to contraindicate the use of Rozerem in all patients with hepatic disease. The increases in AUC in mild hepatic impairment are small and should not result in serum concentrations

outside of the range associated with the doses studied in the clinical trials; and at those doses there were no major safety concerns and there was no evidence of excessive somnolence on the mornings after treatment.

I do not think that it is necessary to reduce the dose for elderly patients, as recommended by Dr. Lee. There were no clinically relevant differences in the safety profiles of the younger and older adult subjects in the clinical safety database. The fact that the previously approved hypnotic products have all had dosing recommendations that included a reduced dose for elderly patients is irrelevant, as Rozerem has a completely different (and novel) mechanism of action from the gabaergic hypnotics. The higher serum concentrations in the elderly subjects that were noted in the pharmacokinetic evaluations, however, should be noted in the package insert.

Based on the data provided by the sponsor in this application, I have concluded that there is a reasonable risk to benefit ratio for Rozerem, if it is used in accordance with the product labeling.

Action recommended by the Division:

Approval

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II, CDER, FDA

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Bob Rappaport
7/18/05 06:13:13 PM
MEDICAL OFFICER

MEMORANDUM

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

DATE: July 14, 2005
TO: DIVISION FILE
FROM: Sara E. Stradley, MS, Regulatory Project Manager
SUBJECT: **Pre-Approval Safety Conference with ODS on July 11, 2005**
Division Wrap-Up meeting
NDA 21-782 Rozerem (ramelteon)

Attendees: Bob Meyer, MD
Bob Rappaport, MD
Leah Ripper
Rigo Roca, MD
D. Elizabeth McNeil, MD
Suresh Doddapaneni, PhD
David Lee, PhD
Eric Duffy, PhD
Ravi Harapanhalli, PhD
Pat Maturu, PhD
Suzanne Thornton-Jones, PhD
Adam Wasserman, PhD
Tom Permutt, PhD
Dionne Price, PhD
Sara Stradley, MS
Sandy Birdsong
Marty Pollack, PhD

The following slides were presented to ODS and Bob Meyer. Elizabeth McNeil presented the Clinical overview, David Lee presented the Clinical Pharmacology overview, and Adam Wasserman presented the Pharm/Tox overview.

Bob Meyer and Bob Rappaport both agreed that approving this drug appears to be the path forward.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 58,136

7/16/04

Takeda Global Research & Development Center, Inc.
475 Half Day Road
Lincolnshire, IL 60069

Attention: Tracy Lynch
Program Manager, Regulatory Affairs

Dear Ms. Lynch:

Please refer to the meeting between representatives of your firm and FDA on June 22, 2004. The purpose of the pre NDA meeting was to discuss the clinical development plan for ramelteon (TAK-375).

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7430.

Sincerely,

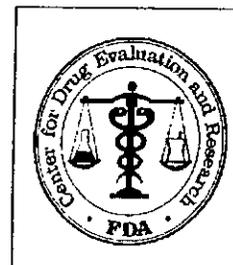
{See appended electronic signature page}

Sara E. Stradley, MS
Regulatory Project Manager
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

Industry Meeting Minutes

Meeting Date: June 22, 2004
Location: Parklawn Building, Conference Room C
IND Name: 58,136
Sponsor: Takeda Global Research and Development
Drug: TAK-375 (ramelteon)
Indication: treatment of insomnia
Type of Meeting: Type B (pre NDA/clinical)
Meeting Chair: Rigoberto Roca, MD, Deputy Division Director
 Division of Anesthetic, Critical Care and Addiction Drug Products, HFD-170



Takeda	Title
Stephen Sainati, MD, PhD	VP, Clinical Research, MPDRAP IIIB
Frank Ogrinic, PhD	Senior Manager, Statistics
Aziz Karim, PhD	VP, Clinical Research, Phase I
David Baron, PhD	Senior Director, Non-clinical Safety and Efficacy
Leslie Koehler, BS, MBA	Assoc Director, Product Development, Regulatory Affairs
Steve Danielson, BS	Manager, Regulatory Affairs
Tracy Lynch, BS	Program Manager, Regulatory Affairs
FDA	Title
Bob Meyer, MD	Director, Office of New Drugs II
Bob A. Rappaport, MD	Division Director
Rigoberto Roca, MD	Deputy Division Director, Medical Team Leader
D. Elizabeth McNeil, MD	Medical Officer
Ravi Harapanhalli, PhD	Team Leader, Chemistry
Dominic Chiapperino, PhD	Chemistry Reviewer
Dan Mellon, PhD	Supervisor, Pharmacology/Toxicology
Adam Wasserman, PhD	Pharmacology/Toxicology Reviewer
David Lee, PhD	Biopharmacology Reviewer
Thomas J. Permutt, PhD	Team Leader, Statistics
Dionne Price, PhD	Statistics Reviewer
Sara Stradley, MS	Regulatory Project Manager
Michael Klein, PhD	Team Leader, Senior Interdisciplinary Scientist, Controlled Substance Staff

Meeting Objective(s): The purpose of pre NDA meeting was to discuss the content and format of the clinical section of the NDA for ramelteon (TAK-375).

General Discussion: Following introductions, the discussion focused on the Sponsor's questions that were included in the May 20, 2004 meeting package. The Sponsor's questions are presented below in italicized text. Agency responses, prepared prior to the meeting and presented on slides, are in italics. Discussion is presented in normal text.

Administrative

Question 1: TGRD believes that approval of ramelteon as the first nonscheduled prescription sleep-promoting agent, one with a completely novel mechanism of action relative to all currently available treatments for sleep disorders, would represent a significant enough therapeutic advance to qualify for a Priority Review, in accordance with MAPP 6020.3, and intends to seek a "P" designation for the review of the NDA. Does the Agency concur that this is a reasonable request? TGRD will provide, in support of the official request for a Priority review, epidemiological data and other information quantifying the potential for decreased adverse events and health risks incident to the availability of a sleep promoting agent that does not act on the GABA receptor complex and that is not a controlled substance.

FDA RESPONSE

We do not concur with the priority designation. We agree that the mechanism of action is novel but we are not convinced that ramelteon eliminates or substantially reduces specific treatment limiting drug reactions.

Discussion

The Division stated that the Sponsor should expand on their rationale for the priority designation. The Division questioned the therapeutic advantage of ramelteon over other hypnotics on the market. The Division stated that if the application were given a priority designation, the Sponsor should be prepared to submit the 120-day safety update and any other information earlier in the review cycle in order to give adequate time for review.

Question 2: Is the comprehensive CTD Table of Contents provided as Appendix D to this briefing document sufficiently detailed to fulfill the TOC requirements in Module 1 of the CTD and facilitate agency review?

FDA RESPONSE

The CMC sections appear sufficient.

The Clinical section appears sufficient.

The Pharmacology Toxicology sections appear sufficient.

Discussion

There was no additional discussion beyond the information provided in the slides.

Question 3: TGRD proposes to submit the review copy in electronic format only. Would this be acceptable?

FDA RESPONSE

Yes

Discussion

There was no additional discussion beyond the information provided in the slides.

Question 4: As recommended by the Agency at the pre-NDA CMC meeting on 15 December 2003, and the 24 September 2003 Memorandum from the Department of Health and Human Services, TGRD is not planning to provide a paper copy of the pertinent application information to the ORA District Office. Instead, TGRD will provide a letter to the home district certifying that the electronic CMC section has been submitted to CDER. Does the Division agree with this approach? We note that the latest Pre-approval Inspection Guidance, revised March 2004, indicates that the FDA district office is expecting three field copies to be submitted at the time of NDA submission. (Please refer to Section F of the PDI Guidance. For ease of reference, this memorandum is attached as Appendix F).

FDA RESPONSE

This is an acceptable approach.

Discussion

There was no additional discussion beyond the information provided in the slides.

Question 5: Does the Agency expect to refer this NDA to an Advisory Committee as part of the review and approval process?

FDA RESPONSE

We are currently considering whether to refer this product to an Advisory Committee. We will alert you as to our final decision in a timely manner.

Discussion

The Sponsor was reminded that if this NDA is granted a priority review (i.e., 6 months), the Sponsor and the Division would need to be fully prepared to discuss both the safety and efficacy information in the application at an Advisory Committee meeting 2-3 months into the review clock.

Question 6: The stability datasets will be placed under Item 11 in the hybrid eNDA. Is this acceptable?

FDA RESPONSE

Item 11 is designated for clinical Case Reports Tabulations (CRTs), so this would not be the appropriate location for stability data.

Electronically submitted stability data pertaining to both the drug substance and the drug product should be in the appropriate subfolders, "substan" or "product", of the CMC folder (Item 4).

Discussion

The Sponsor was advised to contact the electronic submissions group for further discussion.

Question 7: In light of the planned September 2004 NDA submission, TGRD requests a waiver (per 21 CFR §312.10[a]) of the requirement to submit an Annual Report for this IND in August. Does the Agency agree that this is acceptable?

FDA RESPONSE

We would grant a one month extension to the requirement for an annual report. We will expect to have either the NDA or an annual report for the IND submitted no later than September 30 2004. If the NDA is submitted in September 2004, the requirement for an annual report will be waived.

Discussion

There was no additional discussion beyond the information provided in the slides.

Question 8: Regarding the submission of the trade label and packaging components:

-TGRD is planning to submit black and white flats of the trade bottle labels, three-tablet sample blister, sample carton, and sample display tray. Is this acceptable?

-If so, at what point during the review process should TGRD expect to submit the final commercial packaging, with colors and logos for review and approval?

FDA RESPONSE

Yes

We would expect the final commercial packaging with colors and logos at least half way through the review cycle so as to initiate a consult to the Office of Drug Safety.

Discussion

The Division clarified that for a 10-month review clock the trade label and packaging components should be submitted not later than 5 months into the review cycle.

Question 9: TGRD is planning to request a deferral of the requirement to conduct insomnia studies in the pediatric population based on the recommendations of the Pediatric Advisory Committee, and as suggested at the End-of-Phase-II meeting on 16 July 2002. Does the Agency agree that a deferral of the requirement for pediatric studies for ramelteon is acceptable?

FDA RESPONSE

We will grant a deferral. Since ramelteon has a novel mechanism of action, we would prefer to have postmarketing safety data from adults before commencing studies in children.

Discussion

There was no additional discussion beyond the information provided in the slides.

Pharmacology/Toxicology

Question 1: The database for nonclinical studies of ramelteon and its principal active metabolite MII is listed in the proposed CTD Table of Contents, Module 4 (Appendix D).

-Do the listed studies support this NDA filing?

FDA RESPONSE

As discussed in the CMC Pre-NDA meeting of 12/15/2003, qualification of several isolated impurities in two in vitro genetic toxicology assays is still required and should utilize concentrations that produce cytotoxicity or reach the upper concentration limit specified in ICH S2A Guidance.

With this exception, the studies listed appear to satisfy the nonclinical study requirements for the filing of an NDA.

Discussion

The Division clarified that if the specifications were tightened to below 0.1%, then no studies would be needed. However, the Division stated that this specification holds for structures that do not contain any structural alerts for mutagenicity. If the structures suggest the potential for increased toxicological risk, the qualification threshold may need to be reduced to below the 0.1% level.

Question 1 (cont.)

-Are the nonclinical studies adequate to support the proposed labeling and chronic use of this compound?

FDA RESPONSE

The chronic studies conducted in rat and monkey are sufficient to support a chronic duration of use. The support for dosing and overall adequacy of these studies will be a review issue, however.

The proposed labeling of this compound will be determined upon consideration of the entire review.

Discussion

There was no additional discussion beyond the information provided in the slides.

Question 2: [

evaluations adequate to support the proposed labeling?

] Are these

The proposed package insert [

]

FDA RESPONSE

- The adequacy of the [] is considered a review issue and will be assessed as part of the NDA review.
- Support for the proposed labeling will depend on the Division's assessment of the explanations submitted by the sponsor and the quality and thoroughness of the [] studies provided. Input will be sought from the Executive Carcinogenicity Committee to determine if they concur with the [] explanations proposed.

Discussion

There was no additional discussion beyond the information provided in the slides.

Question 3: TGRD will be providing the following SAS transport files in the required e-NDA format for the rodent carcinogenicity studies M-11-00560, M-11-00561:

-Animal Tumor Data Set: ANIMAL.XPT

Includes header information, animal tumor data set, tumor type code data set and organ/tissue code data set

-Body Weight Data Set: WEIGHT.XPT

-Food Consumption Data Set: FOODCON.XPT

Will the Agency require any other nonclinical datasets to aid in the review of the application?

FDA RESPONSE

We do not require any additional nonclinical datasets to be submitted

Discussion

There was no additional discussion beyond the information provided in the slides.

Additional Comments:

•Please provide a justification for the adequacy of dose selection for both rat and mouse carcinogenicity bioassays as protocol concurrence from the Executive Carcinogenicity Assessment Committee was not obtained. This justification should take into account and reference the ICH Guidelines for dosing in carcinogenicity studies.

•Please provide a metabolite comparison between nonclinical species and humans which delineates the exposure margin(s) in nonclinical species of observed human metabolites.

•Please provide all referenced literature cited to support nonclinical pharmacology/toxicology conclusions in electronic format.

Discussion

The Division clarified that the metabolite comparison should be done without regard to whether it is an active metabolite or not.

Human Pharmacology

Question 1: Are the pharmacokinetic and metabolic characterizations of ramelteon adequate for filing?

FDA RESPONSE

The described pharmacokinetic and metabolic characterizations of ramelteon appear to be adequate for filing the NDA.

Discussion

There was no additional discussion beyond the information provided in the slides.

Question 2: TGRD does not plan to include a CYP1A2 class restriction on ramelteon based on the drug-drug interaction data. Does the Agency agree?

FDA RESPONSE

Agency is unable to agree at this time pending thorough review and understanding of this data and the risk/benefit ratio of the drug.

Discussion

There was no additional discussion beyond the information provided in the slides.

Question 3: Will the Agency require datasets from the BA study?

FDA RESPONSE

Please submit the datasets for all studies.

Discussion

The Division clarified that datasets should be submitted for all PK studies.

Clinical

Question 1: TGRD intends to utilize the data from the primary efficacy trials 017, 021, 023, and 025 and supportive efficacy trials 002 and 005 to support the following proposed indication: "Ramelteon is indicated for the treatment of insomnia."

3. Are these studies adequate to support a — indication of insomnia in the nonpediatric population?

FDA RESPONSE

The studies will support submission of a New Drug Application.

We will need to formally review the studies to determine whether they will support the desired indication.

Discussion

There was no additional discussion beyond the information provided in the slides.

Question 2: Based on the supportive information provided in the application, ramelteon should be considered the first candidate in a new class of sleep promoting compounds, with a mechanism of action distinct from the sedative hypnotics. Does the Agency agree?

FDA RESPONSE

We agree that ramelteon appears to have a novel mechanism of action, which is unlike currently marketed sedative-hypnotics.

Discussion

There was no additional discussion beyond the information provided in the slides.

Question 3: Since the safety profile and mechanism of action of this new class of compounds are distinctly different than that of the sedative-hypnotics, TGRD proposes to remove the following elements considered 'class labeling' of sedative-hypnotics that are not applicable to ramelteon.

- "Hypnotics should generally be limited to 7 to 10 days of use, and reevaluation of the patient is recommended if they are to be taken for more than 2 to 3 weeks."*
- "... should not be prescribed in quantities exceeding a 1-month supply"*
- "A variety of abnormal thinking and behavior changes have been reported to occur in association with the use of sedative hypnotics..."*
- "It can rarely be determined with certainty whether a particular instance of the abnormal behaviors described above is drug-induced..."*
- "Following the rapid dose decrease or abrupt discontinuation of sedative hypnotics, there have been reports of signs and symptoms similar to those associated with withdrawal from other CNS-depressant drugs."*

Does the Agency agree that the removal of these portions of class labeling is appropriate? (Refer to the draft ramelteon label. Appendix H).

FDA RESPONSE

The labeling details will be a review issue. We would be willing to modify the labeling if the provided data is supportive of our doing so.

Discussion

There was no additional discussion beyond the information provided in the slides.

Question 4: Do the data provided adequately justify the dose recommendation for adults and elderly?

FDA RESPONSE

While the data appears to be adequate, this is a review issue. As an example, it is noted that the incidence of adverse effects was lowest in the group which took more than 16 mg, though this might be an artifact of the small sample size (meeting package, page 061). It is also noted that in the transient insomnia model, LPS seemed to increase slightly with higher doses (meeting package, page 044). A detailed review of the study data will allow us to determine whether we concur with the choice of dose.

Discussion

There was no additional discussion beyond the information provided in the slides.

Question 5: TGRD will be providing SAS transport files from the U.S. efficacy studies (002, 005, 017, 020, 021, 023, 025). Does the Agency agree with the selection of studies?

FDA RESPONSE

We agree with the studies selected but we would also like the SAS transport files for studies 031, 031 and 022 (endocrine effect studies)

We reserve the right to ask for additional SAS transport files if we find that we need that data to evaluate efficacy and safety.

Discussion

The Division noted that the first point on the slide should have stated-

We agree with the studies selected but we would also like the SAS transport files for studies 031, ~~031~~, 032, and 022 (endocrine effect studies)

Question 6: TGRD is planning to provide SAS transport files containing raw data, including subject demographic characteristics and treatment assignments, and additional derived variables as suggested in Appendix 2 of the FDA Guidance for Industry "Providing Regulatory Submissions in Electronic Format - NDAs", FDA, CDER, IT3, 1999". Is this acceptable?

FDA RESPONSE

It is acceptable to provide the data in the manner suggested by the referenced guidance.

Discussion

There was no additional discussion beyond the information provided in the slides.

Question 7: TGRD is planning to provide SAS transport files with datasets for "Efficacy" containing subject demographic characteristics and treatment assignments, the primary and secondary efficacy variables, the variables used in calculations of the primary and secondary variables, and the variables indicating an observation used for particular analyses. Is this acceptable?

FDA RESPONSE

Yes, the plan is acceptable.

Please make certain that each patient has a unique identifier that may be used to trace him/her through all datasets and studies in which he/she participated.

Discussion

The Sponsor stated that unique identifiers have been included. The Division asked for clarification on the SAS transport files. The Sponsor clarified that the data definition format will include CRF, physical exam, adverse events etc.

Question 8: What is the maximum permissible size of SAS data sets? Does the agency have a preference for how data sets that exceed this limit are split? For example, the laboratory, sleep diary, and pooled safety datasets are likely to need to be split, and we would like to do so in a manner that best facilitates review by the agency.

FDA RESPONSE

Divide datasets that are larger than 25 MB into smaller datasets. For example, clinical chemistry data may be further divided by specific lab tests. A dataset type should not be divided unless the size is greater than 25 MB and, when dividing a dataset type, it should be done with the fewest number of overall datasets. You should discuss the organization of the datasets with the eSub group. File names should include the three character extension .xpt to be compatible with our desktop set up and training.

Discussion

There was no additional discussion beyond the information provided in the slides.

Question 9: A sample format for SAS data definitions is included for review as Appendix I. Is this format acceptable?

FDA RESPONSE

Please clarify. Is Appendix I meant to depict a data definition table?

In general, data definition tables should include the variable name, a description of the variable, the type of variable (e.g., numeric, character), and any codes used.

Discussion

The Sponsor stated that the wrong attachment was included in the meeting package. The Sponsor stated that their data definition table does not exactly match the Guidance because they have not included links to the location of the variables on the CRF. The Division suggested that the Sponsor send the data definition tables for comment as a Post Meeting Note. The Division stated that the links to the CRF should be included in the table, and the Sponsor stated that they will evaluate how to add this to the table.

POST MEETING NOTE: The sample data definition tables (below) are acceptable, assuming that the links to the CRF are provided under the column labeled "Origin" within the tables.

**Derived Datasets Specifications 2/26/2004
TAK-375-017**

Program Name	DIAE.SAS
Data Set Name:	DAE
Label:	Adverse Event
Structure	One Observation per patient per Adverse Event

* Variables are repeated in all datasets and created in DDEMO dataset.

Variable	Type	Len	Format	Label	Origin	Detail
STUDY	Char	20		Protocol Number	Ae.study	
CENTRE	Char	10		Centre	Ae.centre	
*PLCENTRE	Char	10		Pooled Centre		See DDEMO for detail.
PATID	Num	8	10.	Subject Identifier	Ae.patid	
*SITESUBJ	Char	30		Site/Subject		See DDEMO for detail.
*SEX	Num	8		Gender		See DDEMO for detail.
*AGE	Num	8		Age at entry (years)		See DDEMO for detail.
*SEQ	Num	8	ROMAN3.	Actual Treatment Sequence		See DDEMO for detail.
*STARTDT	Num	8	DATE9.	Start date of double-blind medication		See DDEMO for detail.
*STARTTM	Num	8	HHMM5.	Start Time of double-blind medication		See DDEMO for detail.
*LASTTRT	Num	8		Last treatment		See DDEMO for detail.
*LASTTRTC	Char	15		Last treatment decoded		See DDEMO for detail.
*LDOSVIS	Num	8		Last Visit on treatment		See DDEMO for detail.
*LDOSVISC	Char	45		Last Visit on treatment decoded		See DDEMO for detail.
*LASTDT	Num	8	DATE9.	Last date of double-blind medication		See DDEMO for detail.
*LASTTM	Num	8	HHMM5.	Last time of double-blind medication		See DDEMO for detail.
*POPITT	Num	8		Intention-to-treat population		See DDEMO for detail.
*EXCLEFF	Num	8		Exclude from efficacy, demo & Sp. Safety		See DDEMO for detail.
*POPPROT	Num	8		Per-Protocol population		See DDEMO for detail.
AEACT	Num	8		Action Concerning Study Drug	Ae.aeact	
AEACTC	Char	24		Action Concerning Study Drug (decoded)		
AEFREQ	Num	8		Frequency	Ae.freq	
AEFREQC	Char	24		Frequency (decoded)		
AEOUT	Num	8		Outcome	Ae.aeout	
AEOUTC	Char	25		Outcome (decoded)		

Variable	Type	Len	Format	Label	Origin	Detail
AERELA	Num	8		Relationship to Study Drug	Ae.aerela	
AERELAC	Char	24		Relationship to Study Drug (decoded)		
AESEV	Num	8		Severity/Intensity of AE	Ae.sesev	
AESEVC	Char	24		Severity/Intensity of AE (decoded)		
AEVT	Char	200		Adverse Event Text	Ae.aevt	
AESDTD	Num	8		Adverse Event Start Date(Day)		
AESDTM	Num	8		Adverse Event Start Date(Month)		
AESDTY	Num	8		Adverse Event Start Date(Year)		
AESTTM	Num	8	TIME5.	Adverse Event Start Time		
AEEDTD	Num	8		Adverse Event End Date(Day)		
AEEDTM	Num	8		Adverse Event End Date(Month)		
AEEDTY	Num	8		Adverse Event End Date(Year)		
AEENTM	Num	8	TIME5.	Adverse Event End Time		
AEONGO	Num	8		Adverse Event Ongoing at Study End	Ae.aeongo	1=Ongoing
AELAB	Num	8		Lab AE	Ae.aelab	1=Lab AE
AEECG	Num	8		ECG AE	Ae.aeecg	1=ECG AE
AENONEN	Num	8		Other Action-None	Ae.aenonen	1=None
AEOMEDN	Num	8		Other Action-Medication	Ae.aeomedn	2=Other Medication
AEHOSPN	Num	8		Other Action-Hospitalization	Ae.aehospn	3=Hospitalization
AEOTHN	Num	8		Other Action-Other	Ae.othn	99=Other
AEOSPY	Char	200		Other Action Specify	Ae.aeospy	
AESER	Num	8		Serious	Ae.aeser	1=Yes. 2=No
AEPNC	Num	8		Preferred Term Code	Ae.aepnc	
AEPN	Char	100		Preferred Term	Ae.aepn	
SOCC	Num	8		SOC Code	Ae.socc	
SOC	Char	100		SOC	Ae.soc	
LLTC	Num	8		Low Level Term Code	Ae.lltc	
LLT	Char	100		Low Level Term	Ae.llt	
AEECLAB	Char	3		ECG or Lab AE	Ae.ecg & Ae.lab	If AE is classified as a LAB or ECG AE set to "YES"; otherwise set to "NO"

Variable	Type	Len	Format	Label	Origin	Detail
RELSTRDY	Num	8		AE start day relative to first dose		Calculated as start date of AE - STARTDT + 1. if Start date of AE < STARTDT then do not add 1
RELSTPDY	Num	8		AE end day relative to first dose		Calculated as Stop date of AE - STARTDT + 1. if Stop date of AE < STARTDT then do not add 1
TRTEMERG	Num	8		Treatment emergent		1 = all AEs with onset dates on or after the start of double-blind dose and no later than 14 days (or 30 days for a serious AE) after the last dose of double-blind medication.
TRT	Num	8		Actual Treatment Received (Num)	Random.trt	Last dose taken at the time of the onset date of the event.
TRTC	Char	15		Actual Treatment Received decoded		

Question 10: FDA guidance requests that all variables be de-coded to their formatted values. TGRD would appreciate agency clarification regarding demographic sub-group variables that are stored in all datasets. For example, gender is stored as both numeric and character (i.e., decoded) in the DEMOG dataset. It is stored in other datasets, however, only as a numeric, and this is true for all subgroup variables. Is this acceptable, or should all subgroup variables be de-coded in every dataset in which they appear?

FDA RESPONSE

Subgroup variables should be decoded in every dataset in which they appear.

Discussion

There was no additional discussion beyond the information provided in the slides.

Question 11: Will the format and outline for CTD Section 2.7.3 Summary Of Clinical Efficacy meet the Division's needs for its review of the efficacy claims? (Refer to Appendix J).

FDA RESPONSE

The format and outline appear acceptable. Of note, the Summary of Clinical Efficacy should conform with the Integrated Summary of Efficacy.

Discussion

The Division provided further clarification. The sponsor stated that their Summary of Clinical Efficacy would conform to the ISE.

Question 12: TGRD is planning on submitting Case Report Forms only for patients who died, had serious adverse events, or who were identified by investigators as discontinuing study participation due to adverse events. Is this acceptable?

FDA RESPONSE

It is acceptable but we remind you that we may request additional data if needed during the review.

It would facilitate the review if you were to provide narratives for patients who died, had SAE or discontinued due to adverse events.

Discussion

There was no additional discussion beyond the information provided in the slides.

Question 13: TGRD is not planning on submitting patient profiles. Is this acceptable?

FDA RESPONSE

This is acceptable.

Discussion

There was no additional discussion beyond the information provided in the slides.

Question 14: Will the format and outline for the IAS meet the Division's needs for its review of the safety claims? (Refer to Appendices K and L).

FDA RESPONSE

The proposed format will meet the Division's needs for the safety review, with the following modifications.

The columns for the adverse event tables should be <4mg, 4mg, 8mg, 16mg, 32 mg, 64 mg, >64 mg.

The columns for the duration of exposure tables and the time to onset of AE tables should be 1 day, >1-7 days, >7 to 35 days, >35 to 180 days, >180 days.

Discussion

The Sponsor asked if the appendix table could contain the dose range and the tables located in the text of the NDA contain the specific dose. The Division stated that the appendices should be formatted to include the specific doses. The Sponsor replied that they do not have their data arranged in such a manner and it may be very time consuming to do so. The Division recommended that the appendices be formatted to include the specific doses and not just ranges. The Division agreed to provide a sample table to the Sponsor (see Post Meeting Note below).

POST MEETING NOTE: Please note these samples are sketches to demonstrate the proper column headers, the rows would have to be fleshed out as appropriate.

Sample event table

	Placebo	<4mg	4mg	8mg	16mg	32 mg	64 mg	>64 mg
Age								
Gender								
Race								
Weight								

Duration of exposure table

	1 day	>1-7 days	>7 to 35 days	>35 to 180 days	>180 days
Age					
Gender					
Race					
Weight					

Time to onset of AE table

	1 day	>1-7 days	>7 to 35 days	>35 to 180 days	>180 days
AE					

Abuse Liability

Question 1: Are the abuse, dependency, and withdrawal data in the NDA sufficient to support a non-scheduled status for ramelteon? (Refer to Appendix M).

FDA RESPONSE

- *This is a review issue.*
- *CSS will review all data submitted in the NDA in assessing the abuse potential of ramelteon and determining whether to recommend scheduling to the Drug Enforcement Administration.*
- *The abuse potential information submitted in Appendix M of the pre-NDA meeting package is insufficient to assess the abuse potential of ramelteon.*
- *An NDA submission should include primary data and full methodologies, including doses of ramelteon that were utilized in the animal and human studies. Additionally, a full binding profile should be submitted in the NDA abuse potential package (see Question 2).*
- *In contrast, the pre-NDA meeting package contained only summaries of methodologies and outcome data, with little information about the doses used.*

- *In November 2001, CSS conducted a review of proposed abuse potential studies, which included summaries similar to those submitted in Appendix M. CSS informed the Sponsor that full protocols, including doses, should be submitted for review, but this information was never submitted.*
- *The Sponsor was also informed that, based on CSS evaluation of completed studies, additional studies may be required if any of the primary data show an abuse potential signal.*
- *Since CSS has not seen any primary data, it is not possible to predict at this time whether ramelteon has abuse potential.*

Discussion

There was no additional discussion beyond the information provided in the slides.

Question 2: The Abuse and Dependence Liability information is integrated throughout the CTD in the appropriate sections and modules. Is this acceptable to the Agency, or is there an alternate or additional format TGRD should use to help facilitate the review? (Refer to Appendix N).

FDA RESPONSE

Under 21 CFR § 314.50 (d) (5) (vii), an NDA is required to contain a separate Abuse Potential Section that includes:

- *Proposal for scheduling and all scientific data that forms the basis of the proposal*
- *Abuse Potential Assessment*
- *Chemistry (including similarity to drugs of known abuse potential)*
- *Pharmacology (clinical and pre-clinical)*
- *Pharmacokinetics and pharmacodynamics*
- *Integrated Summaries of Safety and Efficacy*
- *Information related to overdose*

Discussion

The Division stated that a separate Abuse Liability section is required. The Sponsor stated that they will compile all of the information into a separate section.

POST MEETING NOTE: The Controlled Substance Staff wants to clarify that the abuse liability assessment of TAK-375 should include evaluation and contribution of active metabolites to the overall effects of the drug.

120-Day Safety Update

Question 1: Will the Agency accept the final clinical study report at the 120-day Safety Update: Study 01-02-TL-375-032, "A Phase III Safety Study To Evaluate The Long-Term Effects Of TAK-375 On

Endocrine Function In Adult Subjects With Chronic Insomnia". We note that the Agency will have reviewed up to 9 months of endocrine data from study 022 prior to the 120-day Safety Update.

FDA RESPONSE

It is OND policy that the NDA should be complete at the time of submission. Since the potential endocrine effects are an important part of the safety evaluation, we will expect the final clinical study reports for all of the endocrine studies as part of the initial NDA submission.

Discussion

The Division stated that Study 032 should be submitted with the NDA. The Sponsor stated that this study was not requested by HFD-120 but was performed as a confirmatory study and questioned the need to submit it with the initial NDA. The Sponsor expressed the concern that inclusion of Study 032 with the initial NDA may delay the NDA submission by more than 3 months.

The Division stated that the best regulatory pathway for a first cycle approval would be to include Study 032 with the initial NDA. However, the Division stated that if the Sponsor is confident that the safety and efficacy findings for Study 022 would be sufficient for a complete review package then the Sponsor would not need to include Study 032. However, the Division noted that they may not reach the same conclusions about the safety findings in Study 022 as the Sponsor did.

Question 2: TGRD plans to submit the long-term safety data for 100 subjects with one-year of exposure at the 120-day Safety Update, based on a commitment at the End-of-Phase II meeting on 16 July 2003. Does the Agency still agree with this proposal?

FDA RESPONSE

We will honor the Agency's previous agreement and review this cohort for safety at the 120-day safety update.

Discussion

There was no additional discussion beyond the information provided in the slides.

Question 3: TGRD would like to submit an additional alcohol drug interaction study along with new proposed labeling for the alcohol interaction section of the label at the 120-day safety update. Based on the justification provided in the briefing document, would the Agency be amenable to review and potential modification of the label based on the available new safety data?

FDA RESPONSE

It is OND policy that the NDA should be complete at the time of submission.

We would not be willing to consider new studies or any new data, other than that previously committed to or data requested by the Division as part of the review, at the 120-day safety update.

Discussion

The Division stated that not submitting the additional alcohol interaction study would not prevent filing of the NDA. The Sponsor stated that their PK/PD study did not demonstrate the expected alcohol related effects and thus they are repeating the study.

The Division reminded the Sponsor that the data submitted to the NDA will be used to write the label.

Action Items

None

Appears This Way
On Original

Appears This Way
On Original

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Sara Stradley
7/16/04 10:30:43 AM

7/6/05

ADRA Rev #1 of Action Package for NDA 21-782 Rozerem (ramelteon) Tablets

Reviewer: Lee Ripper, HFD-102

Date received: July 1, 2005

Date of review: July 6, 2005

Date original NDA received: September 22, 2004

UF goal date: July 22, 2005

Proposed Indication: Treatment of insomnia. ⌢

J

Action type: No letter rec'd. RPM clarified that she is waiting for Division/Office decision on action. *Draft AP letter rec'd 7/18/05*

RPM: Sara Stradley

Drug Classification: 1S

505(b)(1) application

Patent Info on form FDA 3542a: Yes

Debarment Certification: AC

Safety Update: Dated 1/20/05, MOR page 134

Clinical Inspection Summary: 4 sites, 6/13/05, final review of the EIR for 2 investigators not completed at time of CIS, all data appeared acceptable.

ODS/DMETS Review of Proprietary Name: 6/21/05 review found "Rozerem" to be acceptable from a safety perspective. MOR and TL reviews did not address tradename. 7/20: *Dr. Meyer to address in Office Director's review.*

DSRCS Review of PPI: N/A

DDMAC Review: 6/21/05 DMETS review stated that DDMAC finds Rozerem acceptable from a promotional perspective.

EA: Applicant requested categorical exclusion.

EER: AC 7/11/05

Financial Disclosure: Acceptable

CMC section to Eric Duffy, 7/7/05

P/T section to Ken Hastings, 7/7/05; review DFS'd 7/13/05

1. 7/6 email to CACurrier and NAKhin: "According to the MOR for NDA 21-782, ramelteon, DSI was contacted (presumably by the MO, Dr. Dawn McNeil) on 4/4/05 re: ⌢

-- a PI who is also ⌢

responsible for

consulted to "contact Dr. — and gain further insight into his role as consultant ⌢

⌢ There is nothing about Dr. — in the 6/13/05 Clinical Inspection Summary.

Can you provide any follow up info on this issue?"

Email from CACurrier dated 7/7/05 states "DSI has not finished the review of the investigation and has not made any conclusion regarding any potential conflict of interest from Dr. — multiple roles. However, even before the investigation assignment issued, it was understood that, even if a conflict of interest existed for Dr. — roles as consultant

and investigator, the data from Dr. [redacted] 4 subjects would not influence the study outcome."

2. 7/6 email to Eric Duffy with question about manufacturer of starting material [redacted]
based on statement in EER. 7/7/05 email from Dr. Duffy clarified that we do not inspect starting materials manufacturing facilities; that, by definition, starting materials need not be manufactured under GMPs.
3. 7/6 email to Sara Stradley. Carton and container labels in the action package are dated 2/2/05. The EDR shows there were at least three later submissions of carton and container labels – which are current? Are the physician samples [redacted] or both? The only PI in the package was from the original submission. There was no letter with the action package – is the division proposing AE or are they negotiating labeling?

7/7/05 email from SStradley clarified that both physician samples are in two presentations for now – [redacted] count sample boxes. Division is reviewing draft labeling dated 9/10/04.
4. 7/6 email to Shirnette Ferguson re: EER status. *EER AC 7/11/05.*
5. I haven't received a draft letter. *Draft AP letter received 7/18/05. Minor comments forward the RPM on 7/20/05.*

Appears This Way
On Original

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Leah Ripper
7/21/05 11:46:37 AM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

6/21/05
Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-782

INFORMATION REQUEST LETTER

Takeda Global Research & Development Center, Inc.
475 Half Day Road
Lincolnshire, IL 60069

Attention: Tracy Lynch
Program Manager, Regulatory Affairs

Dear Ms. Lynch:

Please refer to your September 21, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ramelteon 8 mg.

We acknowledge your March 23, 2005 submission which contained a request for the tradename review of $\text{C} \quad \text{J}$ and Rozerem.

The Division of Medication Errors and Technical Support (DMETS) has reviewed the submission and has the following comments. We request a prompt written response in order to continue our evaluation of your NDA.

TRADENAME

1. The proposed tradename, $\text{C} \quad \text{J}$ is not acceptable due to look-alike and/or sound-alike confusion with Actonel and Abenol.
2. The proposed tradename, Rozerem, is acceptable.

CARTON and CONTAINER LABELS

Revise the established name to comply with USP naming guidelines, which indicates the dosage form should be adjacent to the established name (see example below).

TRADENAME
(ramelteon tablets)
8 mg

If you have any questions, call Sara E. Stradley, Regulatory Project Manager, at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Parinda Jani
6/21/05 06:44:31 PM

6/21/05

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)**

DATE RECEIVED: March 28, 2005	DESIRED COMPLETION DATE: June 17, 2005	ODS CONSULT #: 05-0081
DATE OF DOCUMENT: March 23, 2005	PDUFA DATE: July 22, 2005	

TO: Bob Rappaport, MD
Director, Division of Anesthetic, Analgesia and Rheumatology Drug Products
HFD-170

THROUGH: Sara Stradley
Project Manager
HFD-170

PRODUCT NAME: [] Rozerem (alternate name) (Ramelteon Tablets) 8 mg	NDA SPONSOR: Takeda Global Research and Development Center, Inc.
NDA#: 21-782	

SAFETY EVALUATOR: Kimberly Culley, RPh

RECOMMENDATIONS:

- DMETS does not recommend the use of the proprietary name, [] However, DMETS has no objections to the use of the proprietary name, Rozerem, from a safety perspective. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.
- DMETS recommends implementation of the label and labeling revision outlined in section III of this review to minimize potential errors with the use of this product.
- DDMAC finds the proprietary names [] and Rozerem acceptable from a promotional perspective.

15/

15/

Denise Toyer, PharmD
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Carol Holquist, RPh
Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: April 15, 2005
NDA# 21-782
NAME OF DRUG: []
Rozerem (alternate name)
NDA HOLDER: Takeda Global Research and Development Center, Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Anesthetic, Analgesia and Rheumatology Drug Products (HFD-170), for assessment of the proprietary names [] and "Rozerem" in regard to potential name confusion with other proprietary or established drug names. Container labels and carton labeling were resubmitted for review and comment. However, the package insert was not resubmitted at this time.

This is the fourth name submission for the drug product of ramelteon. On February 7, 2005, DMETS reviewed the proposed name [] and found the name unacceptable due to orthographic similarities with Boniva. The sponsor submitted [] concurrently with [] which was found unacceptable by the Division of Drug Marketing, Advertising and Communications due to promotional concerns. DMETS previously reviewed the proprietary name, [] on January 14, 2004 (ODS consult #03-0251) and found the name acceptable. Upon re-review of the proprietary name on November 19, 2004 (ODS consult #03-0251-1), DMETS found the name acceptable contingent upon approvability of the proprietary name, Lunesta. Due to the similarities in name and product characteristics between [] and Lunesta, the names could not co-exist. Lunesta attained approval on December 15, 2004.

PRODUCT INFORMATION

Ramelteon is a selective melatonin receptor agonist with high affinity for melatonin MT1 and MT2 receptors, which is believed to account for the sleep promoting qualities. Ramelteon is indicated for the treatment of insomnia, [

] Ramelteon is not a controlled substance and there were no cases of overdose reported during clinical development. The recommended dose is one 8 mg tablet to be taken within thirty minutes of bedtime. Ramelteon will be available as 8 mg tablets, with the approved proprietary name printed on one side and "8" on the other. The product will be available in bottles of 30, 100 and 500 tablets.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases³ for existing drug names which sound-alike or look-alike to [] Rozerem to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁴. The Saegis⁵ Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary names [] and Rozerem. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary names [] and Rozerem acceptable from a promotional perspective.
2. The Expert Panel and independent analysis identified five proprietary names that may be potentially confused with [] The products are listed in table 1 (see page 4), along with the dosage forms available and usual dosage.
3. The Expert Panel and independent analysis identified six proprietary names that may be potentially confused with Rozerem. The products are listed in table 2 (see page 5), along with the dosage forms available and usual dosage.

Appears This Way
On Original

¹ MICROMEDEX Integrated Index, 2005 MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-05 Drugs@fda.gov, and the electronic online version of the FDA Orange Book.

⁴ WWW location <http://www.uspto.gov/tmdb/index.html>.

⁵ Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

1 Page(s) Withheld

 ✓ § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

Table 2: Potential Sound-Alike/Look-Alike Names for Rozerem Identified by DMETS Expert Panel and Independent Analysis

Product Name	Established name, Dosage Form(s), Strength(s)	Usual adult dose*	Other**
Rozerem™	Ramelteon Tablets, 8 mg	8 mg 30 minutes prior to bedtime.	
Remeron® Remeron SolTab®	Mirtazapine Tablets, 15 mg, 30 mg, 45 mg Oral Disintegrating Tablet, 15 mg, 30 mg and 45 mg	15 mg/day administered in a single dose, up to a maximum of 45 mg/day.	LA
Regranex®	Beclaplermin Gel, 100 mcg 2 gram , 7.5 gram, and 15 gram multi-use tubes	The amount to be applied will vary depending on the size of the ulcer area.	LA
Rosaderm™ Cleanser	Sodium Sulfacetamide and Sulfur Emulsion, 10%/5% 170 gram tube	Cleansing of the skin should be as frequent as necessary to insure intimate contact with the medication.	LA/SA
Roferon® A	Recombinant Interferon Alfa-2A Solution for Injection, 3 Million International Units 6 Million International Units 9 Million International Units in Prefilled Syringes	Subcutaneous use. Chronic hepatitis C: 3 million IU 3 times/week administered for 12 months. Hairy cell leukemia: Induction dose of 3 million IU daily for 16 to 24 weeks, then maintenance of 3 million IU 3 times/week. CML: Chronic phase Ph-positive CML: Induction dose of 9 million IU daily. Children (CML): Doses seen between 2.5 to 5 million IU/m ² /day given IM. In another study, severe adverse effects including death were noted in children with previously untreated Ph-negative juvenile CML who received interferon doses of 30 million IU/m ² /day.	LA
Romazicon®	Flumazenil Injection 0.1 mg/mL 5 mL and 10 mL Vials	Reversal of Conscious Sedation and Reversal of General Anesthesia: Adults- 0.2 mg intravenously over 15 seconds, may repeat a 2 nd dose after 45 seconds and 60 seconds, up to four doses. Pediatrics- 0.1mg/kg (up to 0.2 mg), repeat up to 4 times if necessary. Benzodiazepine overdose management: 0.2 mg IV over 30 seconds, may repeat in 30 seconds at a dose of 0.3 mg (administered over 30 seconds) with a further dose of 0.5 mg may be administered over 30 seconds at 1 minute intervals, up to cumulative dose of 3 mg.	LA
Zonalon®	Doxepin HCl Cream, 5 %	Apply a thin film of cream 4 times each day with at least a 3 to 4 hour interval between applications.	LA

*Frequently used, not all-inclusive.

**L/A (look-alike), S/A (sound-alike)

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to [] and Rozerem were discussed by the Expert Panel (EPD).

C. PRESCRIPTION ANALYSIS STUDIES

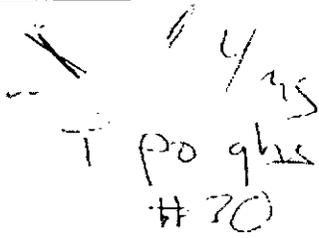
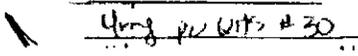
Methodology:

Six separate studies were conducted (3 for each proposed drug name) within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of [] Rozerem with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. Each set of three studies employed a total of 122 health care professionals (pharmacists, physicians, and nurses) for each. This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written for each name, which consisted of a combination of marketed and unapproved drug products and a prescription for [] and Rozerem (see below and page 5). We note that the orders were written for the 4 mg strength of L

The prescriptions were optically scanned and one was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail, which were sent to a random sample of the participating health professionals for their review and interpretation. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

1. []

a. STUDIES

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p><u>Outpatient RX:</u></p> 	<p>[] 4 mg She's to take one po hs Dispense number 30</p>
<p><u>Inpatient RX:</u></p> 	

b. RESULTS

None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. See appendix A for the complete listing of interpretations from the verbal and written studies.

2. ROZEREM

a. STUDIES

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p><u>Outpatient RX:</u></p> <p><i>Rozerem 8mg</i> <i>1 po qhs</i> <i>#70</i></p>	<p>Rozerem 8 mg One po qhs Dispense number 20</p>
<p><u>Inpatient RX:</u></p> <p><i>Rozerem 8mg po qhs #70</i></p>	

b. RESULTS

None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. See appendix B for the complete listing of interpretations from the verbal and written studies.

D. SAFETY EVALUATOR RISK ASSESSMENT

1. []

In reviewing the proprietary name [] the primary concerns related to look-alike and

T

7

2. Rozerem

In reviewing the proprietary name Rozerem, the primary concerns related to look-alike and sound-alike confusion with Remeron, Regranex, Rosaderm Cleanser, Roferon A, Romazicon and Zonalon. Upon further review of the names gathered from EPD and independent analysis, the name Zonalon was not reviewed further due to a lack of convincing look-alike similarities with Rozerem; in addition, there are numerous differentiating product characteristics such as the product strength, indication for use, frequency of administration, route of administration and dosage formulation.

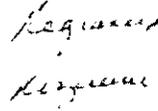
Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Rozerem.

- a. Remeron may look like Rozerem when scripted. Remeron contains mirtazapine in a tablet formulation for the treatment of depression. Remeron is available as 15 mg, 30 mg and 45 mg tablets and orally disintegrating tablets (SolTab). The recommended dose is 15 mg per day, preferably in the evening. Doses may increase to a maximum of 45 mg per day. The orthographic similarities stem from the shared leading "R" and central "er", which is compounded by the possibility for the "m" of Remeron to look like the "z" of Rozerem, when the "z" is written without a downstroke. In addition, the names end in "n" and "m", which appear identical when scripted. However, if the prescriber chooses to write the "z" with a downstroke, this may prove to differentiate between the two names.



The products share the characteristics of route of administration (oral), dose regimen (one tablet daily or one tablet at bedtime), dosage form (tablet), and dispensing amount (one month supply, 30 tablets). However, the principle difference is the lack of overlap in strength (15 mg, 30 mg and 45 mg compared to 8 mg). Although Rozerem could be written without a strength with accurate order completion, orders for Remeron must indicate the strength requested (15 mg, 30 mg and 45 mg). Due to the differing strengths of Remeron, DMETS believes the possibility for confusion to be minimal.

- b. Regranex may look like Rozerem when scripted. Regranex contains becaplermin in a gel formulation for the treatment of diabetic neuropathic ulcers. Regranex is available as a 100 mcg gel to be refrigerated and packaged in 2 gram, 7.5 gram and 15 gram tubes. Patients should apply the gel once daily until complete healing has occurred. The amount of Regranex to be applied depends on the size of the ulcer area (length and width); these measurements are applied to a formula provided by the sponsor in the package insert. The orthographic similarities stem from the shared leading "R" with the subsequent downstroke of the "g" of Regranex and "z" of Rozerem (see below).



The image shows two lines of handwritten cursive text. The top line is 'Regranex' and the bottom line is 'Rozerem'. The focus is on the 'g' in 'Regranex' and the 'z' in 'Rozerem', which both have a similar downstroke that curves back to the right, making them look alike when written quickly.

The similar appearance of the names may lead to confusion due to the overlapping directions for use (daily) and single strength status. Due to the single strength status, it is not necessary for a practitioner to indicate strength for accurate order completion. In addition, prescriptions for Regranex may be written without indicating the amount to be applied, as each wound will vary in size and shape, and the directions for wound care will be extensive and most likely not fit on a written prescription or pharmacy label. If specific and/or detailed instructions are omitted or the phrases such as 'use as directed or use daily as directed' are presented on the prescription, this may not cue the practitioner as to the identity of the drug especially since Regranex and Rozerem may be orthographically similar when scripted. However, the drug products will differ in prescribing quantities [#1 (tube), 2 g, 7.5 gm or 15 g tube compared with one month supply or number of tablets], storage criteria (refrigeration compared to room temperature), and route of administration (topical compared with oral). Although, the possibility for an overlap at the number "15" exists, the prescriber will likely indicate gram (gm) or the number sign (#) upon scripting, which should help to distinguish the products. To get to this point of confusion, the practitioner would have to write "UD" or "daily/QD" as the directions for use; which for sleeping aids is not common as the practitioners typically want to differentiate this specific medication by the use of directions such as "use at bedtime/qhs." Furthermore, the pharmacist must misinterpret the name, the order amount and directions for use on a prescription order for an error to occur. The specificity of Regranex use may also diminish confusion as it is ordinarily used in the hospital setting and administered by the physician. Outpatient pharmacies will not likely stock the medication due to increased cost and low usage, thus creating another method to distinguish the products. Due to the low likelihood of product characteristic overlap and the specificity of use of Regranex, DMETS believes the possibility for confusion to be minimal.

- c. Rosaderm Cleanser may look and sound like Rozerem when scripted and spoken. Rosaderm contains sodium sulfacetamide and sulfur as a cleanser in a 170 gram tube. Rosaderm is a cleansing product used to treat acne. The product should be used as frequent as necessary to insure intimate contact with the medication. The orthographic similarities stem from the shared "Ro", central "er" and concluding "m." Furthermore, the "s" of Rosaderm may look similar to the "z" of Rozerem (see page 12). However, the upstroke of the "d" of Rosaderm should help to differentiate the two names. The phonetic similarities route in the shared leading "Roz" sound, central "ä" and concluding

"m". However, the concluding "derm" of Rozaderm and the "rem" of Rozerem should help to differentiate the names in speech.

Rozaderm
Rozerem

Although the products share single strength status, they differ in all other characteristics as shown by the following: dosage regimen (apply as needed compared to one tablet/one at bedtime), dosage form (emulsion compared to tablet), dispensing amount (number one tube or 170 grams compared to number of tablets), and route of administration (topical compared to oral). Due to the lack of convincing look-alike and sound-alike similarities and the differing characteristics, DMETS believes the possibility for confusion to be minimal.

- d. Roferon A may look like Rozerem when scripted. Roferon A contains interferon alfa-2a in prefilled syringes for the treatment of chronic hepatitis C and hairy cell leukemia in patients over the age of eighteen. Roferon A is available as 3 million units, 6 million units and 9 million unit prefilled syringes that should be stored under refrigeration. The recommended dose for chronic hepatitis is 3 million units three times a week administered subcutaneously for 12 months. The patient may undergo an induction dose of 6 million units three times per week for the first 3 months followed by 3 million units three times per week for 9 months. The recommended initial dosage for chronic myelogenous leukemia is 9 million units daily, but the optimal dose and duration of therapy have not yet been determined. The recommended induction dose for hairy cell leukemia is 3 million units daily for 16 to 24 weeks with the maintenance dose of 3 million units three times per week. The orthographic similarities stem from the shared leading "Ro" and central "r", which are compounded by the likeness of the concluding "n" and "m", and the downstroke of the "f" and "z" (see below).

Roferon
Rozerem

The products differ in the following characteristics: route of administration (subcutaneous compared to oral), strength (3, 6 and 9 million units compared to 8 mg), dosage regimen (3-9 million units three times per week or 3 million units daily compared to 8 mg/one tablet daily or at bedtime), dosage form (prefilled syringe for subcutaneous injection compared to tablet), and storage (refrigeration compared to room temperature). Furthermore, due to the disease to be treated, the patients will be under close supervision of care, which will also serve to alleviate confusion. Although reference can be made to the likeness of "3" as in 3 million Roferon and "8" of Rozerem, the differing frequency of dosing and dosage form should help to reduce possible confusion. Thus, due to the differing characteristics, DMETS believed the possibility for confusion to be minimal.

- e. Romazicon may look similar to Rozerem when scripted. Romazicon contains flumazenil as an injectable formulation for the complete or partial reversal of the sedative effects of benzodiazepines. This may be in the context of general anesthesia induced and/or maintained with benzodiazepines, sedation produced with benzodiazepines for diagnostic and therapeutic procedures, or the management of benzodiazepine overdose. The dose depends on indication, but ranges from 0.2 mg to 0.5 mg administered intravenously to be repeated at various doses, if needed. The orthographic similarities stem from the shared lead "R" with possibility for the "ze" of Rozerem to resemble the "m" of Romazicon (see page 13). In addition, the concluding "con" of Romazicon may appear like the "rem" of Rozerem. However, Romazicon appears longer than Rozerem due to the difference in letter count (nine compared to seven).

The products share single strength status, but this should not be an applicable similarity in light of the clinical use of Romazicon. Due to Romazecon's indication of use and necessity for repeat dosing for the desired effect, practitioners will "urgent order" a vial or use a stock vial. Hence, the physician (anesthesiologist) will have Romazicom on hand prior to anesthesia. For situations on the general medicine floor or the emergency room that would be categorized as serious (accidental/intentional overdose), the physician will "urgent order" a vial from the pharmacy or more likely, pull it from floor stock (i.e. Pyxis). In addition, the drug products differ in dosage regimen (0.2 to 0.5 mg, to be repeated as needed compared to one tablet/one at bedtime), dosage form (injectable compared to tablet), and route of administration (intravenously compared to oral), which would also alleviate confusion in the hospital. Due to this context of use plus the differing product characteristics, DMETS believes the possibility for confusion to be minimal.

III. COMMENTS TO THE SPONSOR:

DMETS does not recommend the use of the proprietary name [] However, DMETS has no objections to the use of the proprietary name Rozerem. []

[

]

t

]

Additionally, DMETS reviewed the labels and labeling from a safety perspective. DMETS has identified one area of possible improvement, which might minimize potential user error.

A. CARTON LABELING AND CONTAINER LABELS

Revise the established name to comply with USP naming guidelines, which indicates the dosage form should be adjacent to the established name (see example below).

ramelteon tablets
8 mg

Appears This Way
On Original

IV. RECOMMENDATIONS:

- A. DMETS does not recommend the use of the proprietary name, [] However, DMETS has no objections to the use of the proprietary name, Rozerem from a safety perspective. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.
- B. DMETS recommends implementation of the label and labeling revision outlined in section III of this review to minimize potential errors with the use of this product.
- C. DDMAC finds the proprietary names [] and Rozerem acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, project manager, at 301-827-1998.

Kimberly Culley, RPh
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, RPh
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

1 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

Appendix B. Rozerem Prescription Study Results

Outpatient Prescription	Inpatient Prescription	Voice Prescription
Rozerem	Rozarem	Verazarem
Rozerem	Rozarem	Rozunan
Rozerem	Rozarem	Verozeram
Rozerem	Rorarem	Rozerem
Rozerem	Rozarem	Rozirem
Rozerem	Rozarem	Verazeron
Rozerem	Rozarem	Rozeram
Rozerem	Rozarem	roseram
Rogerem	Rozaren	Ferozeram
Rozerem	Rosarem	Rozarem
Rozerem	Rorarem	Roserem
Rozerem	Rozarem	Thorazoran
Rozerem	Rozarem	Corazoram
Rozerem		

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Kimberly Culley
6/21/05 09:21:55 AM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
6/21/05 09:33:19 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
6/21/05 12:04:03 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
6/21/05 04:27:04 PM
DRUG SAFETY OFFICE REVIEWER

13 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

Stradley, Sara

From: Stradley, Sara
Sent: Thursday, June 16, 2005 1:58 PM
To: 'tlynch@tgrd.com'; 'sdanielson@tgrd.com'
Cc: Stradley, Sara
Subject: CMC response

Tracy

Here is our response to your June 15, 2005 CMC submission regarding the email from the Division on June 10, 2005. Let me know if you have any questions.

In response to an email received on June 10, 2005 providing questions from the CMC reviewer, Takeda Global Research & Development Center, Inc. has the following clarification requests to ensure that our responses are adequate:

Drug Substance Clarifications:

Question 2. Provide process development batch records for [REDACTED]

Process development records are written in Japanese in laboratory notebooks and will need to be translated into English. Is it acceptable to provide a detailed summary of the [REDACTED] experiments performed. [REDACTED]

Evaluation: Yes, it is acceptable to provide now a detailed summary of [REDACTED] experiments [REDACTED]. The process development records supporting this summary (translated into English) needs to be submitted to the NDA file within 3 months.

Question 3. The current submission indicates that written manufacturing directions for [REDACTED] were provided to your contractors, and [REDACTED] supplied by [REDACTED] was used to make Ramelteon API which was used in preclinical safety studies, and [REDACTED] supplied by [REDACTED] was used to make Ramelteon API which was used in clinical studies, and there were no comparability protocols. Provide missing written manufacturing directions for [REDACTED] which were provided to your contractors, and justify that [REDACTED] Ramelteon API.

Takeda would like clarification regarding this request since the information on [REDACTED] provided in the application is consistent with the Agency's direction provided at the pre-NDA meeting. Also, the agency's request is not consistent with our understanding of the information to be provided for a starting material as described in the January 2004 Draft Guidance: Drug Substance Chemistry Manufacturing and Controls Information

Evaluation: You have two options. One is to set the starting material specifications for related substances at non-significant levels [REDACTED]. Second is to

provide written manufacturing directions for — which were provided to all contractors.

Question 9. Include [] specification for Ramelteon []
]

A detailed [] is discussed in section 3.2 S.3.1 (Report M-11-00693 p.27) In all screening experiments. [] ramelteon was observed. Additional [] data generated throughout stability studies described in section 3.2 S.7.1 have also shown that the [] ramelteon is consistent over time. [] was considered as a possible specification, but after considering decision tree# 4 of ICH Q6A, it was concluded. [] specification was not required. Can the agency please explain what additional data is needed to further support the use of decision tree #4 to justify [] specification []

Evaluation: [] was used to investigate the [] of API [] to study the [] in the first report (M-11-00693), and [] was monitored at one time point to investigate the [] for the desired [] in the second report (3.2.S.7.1). — ' specification for the API is commonly requested for other APIs and is simple routine test that justifies desired [] Please include now.

Drug Product Clarifications:

Question 3. There is no [] data to justify that []

[] The content analysis of Ramelteon tablets by [] is not a sensitive test method for the regulatory purpose

The last sentence comments on the acceptability of [] for content. Please clarify what specific test this comment refers to.

Evaluation: This is a two part question where you have asked for clarification for the second part, relating to the — test [] The submission reports that [] was used for [] testing of one sample per location and for [] testing. You need to provide the bridging data for [] methods to justify statistical comparability based on individual values.

Question 4. The current acceptance specification for dissolution for Rameiteon tablets need to be set as Q of — at 15 min for stability. Customary tests [] have to be included in the specifications of Rameiteon tablets.

The justification of the dissolution specification at — minutes was discussed extensively in the NDA (3.2.P.5.6, report M-11-00806, p.8). This justification demonstrated that the variability at 15 minutes makes this time point inappropriate for rameiteon tablets.

Additionally, a Q of — at 15 minutes []

] . The proposed specification of Q=— at — minutes is consistent with the definition of rapidly dissolving (Guidance for Industry, Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on Biopharmaceutics Classification System, August 2000), which is — of label claim dissolved within — minutes. Since this request is not consistent with our understanding of the BCS guidance, could FDA please clarify the basis for the dissolution request so that Takeda can prepare an informed response?

Evaluation: Process capability (tableting) relative to performance specification (Q) was judged by estimating the area under the fitted curve for individual tablets.

Multidisciplinary inputs (medical, chemistry, biopharm, statistics) are used for Q.

Passing Q of — at 15 min with S-2 sampling plan is possible for individual tablets. At lot release time, Q mean values are in the range [] with S-1 sampling plan, and the proportion of the scores above — for individual tablets is only []

The proportion scores drops with [] Desired process capability is at least — method is used for Q, as per the submission. If one has used [] (alternate method) and different performance specifications, then the acceptability of batches based on proportion score will be higher to justify process capability.

Question 5. Revise the expiry date for Rameiteon 8 mg tablets from — months based on a dissolution specification of Q of — at 15 min for stability and/or the observed worst case scenario for full commercial scale batches.

**Appears This Way
On Original**

Please refer to clarification request for comment 4. Additionally, instruction to use commercial scale batches only is at variance with the application in which pilot and commercial scale batches were used to justify expiry. The data provided in the application consists of the following:

	Number of Lots	Long Term Conditions	Intermediate Conditions	Accelerated Conditions
Supportive Data	1		/	/
Pilot Scale	3		/	/
Commercial Scale	3		/	/

The data package provided is in excess of the site-specific requirements set forth in the 1998 guidance titled: *Stability Testing of Drug Substances and Drug Products*. This guidance requires a simple dosage form such as ramelteon to have 3 months of accelerated and long term data on 1 site-specific batch in the application. In addition, the data package provided is more extensive than the recommendations from the September 22, 1999, meeting of the Site-Specific Subcommittee, Advisory Committee for Pharmaceutical Science. One of the advisory group's recommendations required only COAs from the validation lots from the commercial site and a certificate of the process validation to be submitted 3 months prior to the PDUFA date. Takeda feels that the data provided demonstrates acceptable stability from both sites, and requests clarification as to why the agency appears to be using only the commercial site data to assess the proposed expiry date.

Evaluation: The current submission indicates high variability between batches and packages. Expiry date setting is also a multidisciplinary input (chemistry, statistics). The observed worst case scenarios for full scale commercial scale is [] expiration date for 30s bottle, when Q is set at — min time point. This interim expiry date of [] may be extended with the accumulation of additional real time data.

Question 7. Provide certificates of analysis for different Ramelteon 8mg tablets batches used to investigate insomnia and a linkage table between the drug product batch no and the clinical protocol no for insomnia (TL 005, 017, 070, 021, 022, 023, 025 and PNF002).

A table linking the lots used in the requested studies is provided in section 3.2 P.2.2 report M-11-00667 (Table 15 page 23-26), which can then be cross-referenced to the batch analysis report in section 3.2.P.5.1, report M-11-00683. Is this sufficient to meet the agency's request or should COAs still be provided?

TGRD can arrange a teleconference to discuss if further discussion is appropriate.

Evaluation: There is a chance to commit an error and an omission while compiling the summary reports cited by you (M-11-00667 and 00683). To respond to internal inquiries in an expedited way, a table correlating COAs for Ramelteon 8mg tablets and corresponding clinical studies using individual tablets values needs to be provided.

Sara E. Stradley, MS

Regulatory Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research
Phone 301-827-7430
Fax 301-443-7068

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Sara Stradley
6/17/05 07:41:35 AM
CSO

7 Page(s) Withheld



 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

6/12/05

Stradley, Sara

From: Stradley, Sara
Sent: Friday, June 10, 2005 3:03 PM
To: 'tlynch@tgrd.com'; 'sdanielson@tgrd.com'; Stradley, Sara
Subject: BioPharm Info Request

Tracy/Steve-

The Agency is in a final stage of evaluating ramelteon's BCS classification, and is seeking information on ramelteon stability in simulated gastric fluid [] and simulated intestinal fluid [].
] You are requested to generate and submit such data if not already available.

Sara E. Stradley, MS
Regulatory Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research
Phone 301-827-7430
Fax 301-443-7068

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Sara Stradley
6/10/05 03:03:41 PM
CSO

Stradley, Sara

From: Stradley, Sara
Sent: Friday, June 10, 2005 12:48 PM
To: 'tlynch@tgrd.com'; 'sdanielson@tgrd.com'; Stradley, Sara
Subject: CMC info request

Tracy/Steve

Attached is a list of CMC deficiencies. Please let me know your time frame for a response. If you need any clarification, we can arrange a telecon for next week.

Drug substance:

1. The current submission indicates that [] Ramelteon API was tested in preclinical and clinical studies but you are proposing [] Ramelteon for US marketing. The current acceptance specifications for the [] needs to be tightened to be consistent with the actual production experience to produce Ramelteon batches which were used in the clinical testing (- lots), and preclinical testing (- lots).
2. Provide process development batch records for [] impurity [] experiments along with the [] to justify the fate of potential impurities in []
3. The current submission indicates that written manufacturing directions for - were provided to your contractors, and - supplied by [] was used to make Ramelteon API which was used in preclinical safety studies, and - supplied by [] was used to make Ramelteon API which was used in clinical studies, and there were no comparability protocols. Provide missing written manufacturing directions for [] which were provided to your contractors, and justify that [] Ramelteon API.
4. The current acceptance specifications for the [] need to be tightened to be consistent with the actual production experience to produce the drug substance batches which were used in clinical testing (-lots), preclinical testing (-lots).
5. The current submission indicates that there is no acceptance criteria for [] Provide [] results for [] the reference [] method validation for purity and related compounds.
6. Provide a justification for monitoring [] and not the [] when the [] Ramelteon batches did not differ from [] but the [] Ramelteon batches did differ by []
7. The submission indicates that [] Ramelteon but they were not monitored for batch release of Ramelteon. Provide a justification for not monitoring, and any literature references that may [] imbalances.
8. Specify the [] and Ramelteon, as a part of proof of chemical structure.
9. Include [] specification for Ramelteon []

10. Provide a revised [] specification for Ramelteon to be consistent with the actual usage of the clinical and preclinical batches and API process capability. Specify the acceptance specifications for individual impurities based on 95% CI for individual values for the [] lots.

Drug product:

1. Compendial testing of the excipients lactose, starch, and magnesium stearate, may not assure their fitness for use in the product performance of Ramelteon 8 mg tablets. Provide functionality related tests, [] which are critical parameters that [] There is no explanation why such critical attributes have not been considered during formulation and manufacturing process development.

2. Provide routine in-process controls to assure [] by using specific assay methods for Ramelteon which is in conformity with the Agency recommendations []

3. There is no process development data to justify that []

[] The content analysis of Ramelteon tablets by [] is not a sensitive test method for the regulatory purpose.

4. The current acceptance specification for dissolution for Ramelteon tablets need to be set as Q of — at 15 min for stability. Customary tests [] have to be included in the specifications of Ramelteon tablets.

5. Revise the expiry date for Ramelteon 8mg tablets from [] based on a dissolution specification of Q of — at 15 min for stability and/or the observed worst case scenario for full commercial scale batches.

6. Provide special design features of the drug product [] if any, and a rationale for their use.

7. Provide certificates of analysis for different Ramelteon 8mg tablets batches used to investigate insomnia and a linkage table between the drug product batch no and the clinical protocol no for insomnia (TL 005, 017, 020, 021, 022, 023, 025 and PNFP002).

Sara E. Stradley, MS
Regulatory Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research
Phone 301-827-7430
Fax 301-443-7068

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Sara Stradley
6/10/05 12:49:36 PM
CSO

Stradley, Sara

From: sdanielson@tgrd.com
Sent: Wednesday, June 08, 2005 5:47 PM
To: STRADLEYS@cder.fda.gov
Cc: tlynch@tgrd.com; ssainati@tgrd.com
Subject: RE: info request

Hi, Sara,

We did not measure prolactin levels in the open-label safety study -022. We did submit data from the controlled [031 (4-week) and -032 (6-month)] studies. Has your team reviewed these data, or are there other data we can provide?

Steve

-----Original Message-----

From: Stradley, Sara [mailto:STRADLEYS@cder.fda.gov]
Sent: Wednesday, June 08, 2005 4:29 PM
To: Lynch, Tracy (TGRD); Stradley, Sara
Cc: Danielson, Steven (TGRD)
Subject: info request

Tracy
When you return to the office, please provide the following:

Clarify whether you did or did not measure prolactin levels during study TL022.

If you did measure prolactin levels, where may we find that data in the 120-day safety update?

Thanks
Sara

-----Original Message-----

From: tlynch@tgrd.com [mailto:tlynch@tgrd.com]
Sent: Tuesday, June 07, 2005 9:43 PM
To: stradleys@cder.fda.gov
Cc: sdanielson@tgrd.com
Subject: Out of the office

Hi Sara,

Our team will be offsite for the next two days (June 8-9). We will have limited access to email. If there is an issue that you need an immediate response to, please feel free to contact me by cell phone at 847-204-2226. I will be accessing my email in the evening.

I wanted to let you know why you might not receive an immediate response through email.

Thanks!

Tracy

PS. Steve Danielson is also available at: 847-404-5968.

###

This message is for the designated recipient only and may contain privileged or confidential information. If you have received it in error, please notify the sender immediately and delete the original. Any other use of the email by you is prohibited.

###

Appears This Way
On Original

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Sara Stradley
6/9/05 07:46:45 AM
CSO

MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
CONTROLLED SUBSTANCE STAFF

Date: June 7, 2005

To: Bob Rappaport, M.D., Director
Division of Anesthetic, Critical Care and Addiction Drug Products
(HFD-170)

Through: Deborah B. Leiderman, M.D., Director
Michael Klein, Ph.D., Team Leader
Controlled Substance Staff (HFD-009)

From: Katherine Bonson, Ph.D., Pharmacologist
Controlled Substance Staff (HFD-009)

Subject: Consult on abuse potential for NDA review
Ramelteon []
NDA 21-782
Treatment of [] insomnia
Sponsor: Takeda Pharmaceuticals, Lincolnshire, IL

Background:

The Division of Anesthetic, Critical Care and Addiction Drug Products (HFD-170) consulted CSS regarding the abuse potential of ramelteon [] previously known as TAK-375. Ramelteon is a highly selective melatonin-1 (ML-1) receptor agonist that is being proposed for use in the treatment of [] insomnia. Ramelteon has been tested in 42 clinical trials at doses ranging from 0.3 to 160 mg. The recommended therapeutic dose will be 8 mg, taken orally before bedtime.

Some medications approved for the treatment of sleep disorders are controlled substances under the Controlled Substances Act (CSA). The Sponsor proposes that ramelteon not be controlled under the CSA, citing the results from non-clinical studies, clinical trials and human abuse potential studies as support for their position that ramelteon lacks abuse potential and should be approved for marketing as a non-scheduled drug.

Conclusions and Recommendations:

Based upon review of data provided by the Sponsor, CSS concludes that ramelteon does not have abuse liability similar to that of other scheduled drugs indicated for the treatment of sleep disorders.

The most salient finding for this conclusion is that ramelteon did not produce rewarding properties in a human laboratory abuse liability study, as evaluated by a battery of subjective measures, at doses that are 2, 10 and 20 times higher than the recommended therapeutic dose. These data demonstrated that the abuse potential of ramelteon is similar to that of placebo.

Ramelteon did not produce any signals from animal behavioral studies indicating that the drug produces rewarding effects. Monkeys do not self-administer ramelteon and it does not induce a conditioned place preference in rats. There is no generalization between the Schedule IV benzodiazepine, midazolam, and ramelteon. Ramelteon did not affect rotorod performance, an indicator of disruption of motor function, nor did it potentiate the ability of the Schedule IV benzodiazepine, diazepam, to interfere with rotorod performance.

Discontinuation of ramelteon in animals or in humans after chronic administration did not produce withdrawal signs. Ramelteon does not appear to produce physical dependence.

Finally, there is little evidence that ramelteon may be used to incapacitate an unwitting individual for the purpose of committing malicious crimes (such as sexual assault) against that individual. Although ramelteon is freely soluble in ethanol and produces initial sedative effects within 1.5 hr after oral administration in clinical patients with insomnia, there is no evidence that ramelteon produces disruptive behavioral effects that would render an individual defenseless or liable to physical assault. Ramelteon does produce an additive effect to the sedation produced by ethanol. However, human studies with ramelteon at doses up to 20 times those recommended for therapeutic use did not induce changes in cognition or motor performance, nor was there any evidence of amnesia or memory impairment.

I. Summary of Data Related to Abuse Potential from Human Studies

A. Human Laboratory Abuse Potential Study

Ramelteon did not produce rewarding properties in a human laboratory abuse liability study, conducted in polydrug abusers with at least one experience with a sedative-hypnotic drug in the past year. At doses of 16, 80 or 160 mg (p.o.) (representing 2, 10 and 20 times the recommended therapeutic dose), ramelteon did not produce statistically significant increases in subjective responses to "good drug effect", "drug liking", "drug strength", "street value" and "willing to pay". In contrast, the Schedule IV

benzodiazepine, triazolam, produced statistically significant increases in each of these subjective measures. Neither ramelteon or triazolam produced adverse events indicative of euphoria. These data suggest that the abuse potential of ramelteon is similar to that of placebo.

B. Adverse Events in Clinical Efficacy Studies Related to Abuse Liability

The most common adverse event reported by patients in clinical trials with ramelteon was somnolence (33% at 16 mg dose, twice the recommended therapeutic dose). Headache was reported by 64% of those patients exposed to 64 mg of ramelteon (8 times the recommended therapeutic dose). No euphoria was reported by patients, even at doses of ramelteon up to 128 mg (16 times the recommended therapeutic dose). There have been no reports of overdose, nor any reports of safety issues at doses up to 160 mg (20 times the recommended therapeutic dose).

C. Physical Dependence Evaluated in Clinical Efficacy Studies

Ramelteon did not produce rebound insomnia following drug discontinuation in three clinical efficacy studies in adults, one of which evaluated elderly patients. Additionally, ramelteon did not produce any other signs of a withdrawal syndrome, as evaluated by the Benzodiazepine Withdrawal Syndrome Questionnaire.

II. Summary of Data Related to Abuse Potential from Preclinical Studies

A. Receptor Binding

Ramelteon is a highly selective melatonin-1 (ML-1) receptor agonist. It does not have a receptor binding profile that is similar to any known drugs of abuse, nor does it bind significantly to any major or minor neurotransmitter system in the brain with the exception of the melatonin receptor. The mechanism of action of ramelteon is not well understood.

B. Metabolites

Four metabolites of ramelteon were identified in rats and monkeys (M-I, M-II, M-III and M-IV), all of which are present in humans. The major metabolite is M-I and the secondary metabolite is M-III, with plasma levels that are between 1/2 to 1/3 those of M-I. M-II does not bind to any receptors associated with known drugs of abuse.

C. Behavioral Studies

The preclinical behavioral studies with ramelteon include self-administration, conditioned place preference and drug discrimination.

Self-Administration

Two self-administration studies were conducted.

In the first study, ramelteon did not induce self-administration (< 10 injections/2-hour session) at a range of doses (0.01 - 0.3 mg/kg/injection, i.v.) in 3 of 4 monkeys trained to self-administer the sedative methohexital (0.1 mg/kg/injection, i.v.; mean of 100 injections/2-hour session). This rate of ramelteon injection was similar to that of saline and suggests that ramelteon does not have significant rewarding effects. However, 1 of the 4 monkeys did self-administer ramelteon at the three lower doses tested (mean of 90-100 injections/session), but at much lower rate when the highest dose was administered (mean of ~50 injections/session). The lack of a dose-response effect in this single monkey suggests that the results may be anomalous.

Given the difficulty in interpreting the first study, a second study was conducted. Ramelteon was not self-administered at a rate that differed from that for vehicle when tested at 0.025 - 0.4 mg/kg/infusion (i.v.) when given access to the drug in a 2-hour session. A similar lack of self-administration was seen when the access period was extended to 24 hours. In contrast, the Schedule II barbiturate, sodium pentobarbital, produced dose-dependent self-administration at 0.5 and 1.0 mg/kg/infusion (i.v.).

Cumulatively, these two self-administration studies suggest that ramelteon does not produce rewarding effects indicative of abuse liability.

Conditioned Place Preference

Ramelteon (3 - 30 mg/kg, i.p.) did not induce conditioned place preference in rats, similar to the response from melatonin (10 - 100 mg/kg, i.p.) or vehicle. In contrast, known drugs of abuse did produce conditioned place preference, including the Schedule II opioid, morphine (1 mg/kg, s.c.), the Schedule IV benzodiazepine, diazepam (5 mg/kg, p.o.), and the Schedule IV benzodiazepine, triazolam (0.5 mg/kg, p.o.). These data are consistent with the monkey self-administration study showing no significant rewarding properties from ramelteon.

Drug Discrimination

In monkeys trained to discriminate the Schedule IV benzodiazepine, midazolam, ramelteon (3.2 - 10 mg/kg, i.v.) did not generalize to the midazolam interoceptive cue (percent bar pressing on midazolam lever < 20%), similar to vehicle responding. Ramelteon did not affect the rate of responding. These data suggest that ramelteon does not have behavioral effects that are similar to those of benzodiazepine sedative-hypnotics.

Ramelteon (3.2 - 10 mg/kg, i.v.) also did not block the discriminative cue (e.g., signs of withdrawal) produced by the benzodiazepine antagonist, flumazenil (0.0032 - 0.32 mg/kg (cumulative dosing)), in rats that were dependent on the Schedule IV benzodiazepine, diazepam. The inability of ramelteon to reverse the effects of a benzodiazepine antagonist suggests that ramelteon does not act through benzodiazepine receptors. These data are consistent with the midazolam discrimination study.

Drug Interaction Studies

Ramelteon did not affect rotorod performance, an indicator of disruption of motor function, nor did it potentiate the ability of the Schedule IV benzodiazepine, diazepam, to interfere with rotorod performance.

D. Physical Dependence

Ramelteon discontinuation did not induce withdrawal-like behaviors or changes in body weight in monkeys following administration of the drug at 10 mg/kg (i.g.) for one year. Additionally, there were no changes in spontaneous behavior during the discontinuation period, nor were there any changes in conditioned response rates to obtain food or to terminate electric shock.

Similarly, no withdrawal-associated behaviors or changes in body weight were seen following discontinuation of ramelteon (200 or 600 mg/kg, in food) in rats treated with the drug for 28 days. In contrast, discontinuation after 28 days from the Schedule IV benzodiazepine, diazepam (300 mg/kg, in food) produced irritability, a decrease in feeding behavior and a decrease in feces, demonstrating a mild withdrawal syndrome.

Thus, the lack of withdrawal-associated behaviors indicates that ramelteon does not produce physical dependence.

Appears This Way
On Original

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Katherine Bonson
6/10/05 11:22:36 AM
PHARMACOLOGIST

Michael Klein
6/10/05 11:32:52 AM
CHEMIST

Deborah Leiderman
6/13/05 05:26:05 PM
MEDICAL OFFICER



JUN 6 2005

Food and Drug Administration
Rockville MD 20857

Renata Shafor, M.D.
San Diego Sleep Disorders Center
1842 Third Avenue
San Diego, California 92101

Dear Dr. Shafor:

Between February 22, and March 15, 2005, Mr. Thomas R. Beilke, representing the Food and Drug Administration (FDA), conducted an inspection and met with you to review your conduct of three clinical investigations of the investigational drug **L** **J** (ramelteon) performed for Takeda Global Research and Development Center, Inc.:

Protocol TL-375-017 entitled: "A Phase III, Randomized, Double-Blind, Placebo-Controlled, Crossover Study to Determine the Safety and Efficacy of TAK-375 in Elderly Subjects With Chronic Insomnia,"

Protocol TL-375-021 entitled: "A Phase III, Randomized, Double-Blind Placebo-Controlled, PSG Plus Outpatient Study to Determine the Safety and Efficacy of TAK-375 in Adults With Chronic Insomnia," and

Protocol TL-375-023 entitled: "A Phase III, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Single-Dose Study of TAK-375 in Healthy Adult Volunteers in a Sleep Lab Model of Transient Insomnia."

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations. We are aware that at the conclusion of the inspection, Mr. Beilke presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. You did not ensure that the investigations were conducted according to the investigational plans (21CFR 312.60).

Protocols TL-375-017 and TL-375-021 stated that, the nights subjects were in the sleep lab, the Visual Analog Scale, the Digital Symbol Substitution Test, the memory recall, and pre-sleep questionnaires were to be completed 1.5 hours prior to habitual bedtime. We note at least 15 instances for four subjects (# 170151, 170152, 170154, and 170155) in protocol TL-375-017 and six instances for three subjects (# 221225, 221238, and 221432) in protocol TL-375-021 where these tests were completed from between 15 to 149 minutes before the subjects' habitual bedtime.

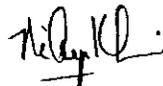
2. You did not maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation (21 CFR 312.62[b]).

Records indicate that three subjects (#170001, 170153, and 170155) in protocol TL-375-017, subject #211434 in protocol TL-375-021, and subject #231063 in protocol TL-375-023 had study-related ECGs performed before they signed the consent form. In addition, records indicate that two subjects (#170001 and 170153) in protocol TL-375-017 had blood samples taken before they signed the consent form. We acknowledge your statement made during the inspection that all subjects signed the informed consent form before any study-related procedures were performed; and that the clocks on the ECG machine and in various places in the Sleep Disorders Center which were used to record study procedures were not set to the correct time. All study equipment, including clocks, should be calibrated prior to study initiation so that study procedures can be accurately reported.

Please make appropriate corrections in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies

We appreciate the cooperation shown Investigator Beilke during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,



Ni A. Khin, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

Page 3 - Renata Shafor, M.D.

CFN/FEI:

Field Classification: VAI

Headquarters Classification:

1)NAI

2)VAI- no response required

3)VAI- response requested

4)OAI

Deficiencies noted:

failure to adhere to protocol (05)

inadequate and inaccurate records (06)

cc:

HFA-224

HFD-170 Doc.Rm. NDA# 21-782

HFD-170 Review Div.Dir. (Rappaport)

HFD-170 MO (McNeill)

HFD-170 PM (Stradley)

HFD-46/47c/r/s/ GCP File #11511

HFD-46/47 (Currier)

HFR-PA252 DIB (Maxwell)

HFR-PA2565 Bimo Monitor (Koller)

HFR-PA2535 Field Investigator (Beilke)

GCF-1 Seth Ray

r/d:cac:6/1/05

reviewed:NK:6/2/05

f/t:cac:6/2/05

o:\cac\2005\Shafor.PDUFA.N21782 L 3LTR.VAI.doc

Reviewer Note to Rev. Div. M.O.

Dr. Shafor enrolled 26, 19, and 27 subjects in protocols TL-375-017, 021 and 023 respectively. The number of subjects that completed each study was 17, 16, and 27 respectively. The study records for 10 subjects in each of the three protocols were reviewed during the inspection. Records examined included source data recording forms, clinical laboratory testing reports, informed consent documents, correspondence with the IRB and sponsor, case report forms, drug accountability records, data listings, and documentation regarding the certification of the PSG machines on site. The review revealed that all subjects met entry criteria, all source data agreed with data in CRFs and data listings, all AEs and intercurrent illnesses were properly reported to the sponsor, and changes to the protocol and consent forms were properly approved and documented by the IRB. Monitoring appeared adequate and drug accountability records reconciled the amount of drug received, dispensed, and returned to the sponsor.

The inspection revealed two violations of FDA regulations; inaccurate case histories, and protocol deviations. The case histories were deemed inaccurate because all clocks at the study site and on the ECG were not set to the same time. It appears as if ECGs and blood draws occurred prior to subjects signing informed consents. This problem was discovered by the site prior to our inspection and a memo to the file explaining the discrepancies in the recorded times was placed in the regulatory binder. The explanation seems plausible, and in any case would not have affected study data. The protocol deviations occurred when the site did not ensure that the VAS scales, DSST tests, memory recall, and pre-sleep questionnaires were completed 1.5 hours prior to habitual bedtime when subjects were in the sleep labs, as was required by protocol -017 and -021. The records showed at least 15 instances where 4 subjects (# 170151, 170152, 170154, and 170155) in protocol T1-375-017 had completed the tests from 33 minutes to 149 minutes prior to lights out, and 6 instances where 3 subjects (# 221225, 221238, and 221432) in protocol 021 had completed the tests from 15 to 71 minutes prior to lights out. Again, it does not appear that the delay in the tests would have affected the validity of the study data, or would have increased subject risk.

From the records reviewed, it appears the data from Dr. Shafor's site (protocols TL-375-017, 021, and 023) could be used to support an approval decision for the NDA.

Appears This Way
On Original

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Ni Aye Khin

6/10/05 01:13:59 PM

Stradley, Sara

From: Stradley, Sara
Sent: Wednesday, June 01, 2005 12:37 PM
To: tlynch@tgrd.com
Cc: Stradley, Sara
Subject: another question

Subject: 12646/221471, —

This 57 year old woman, died on Study Day — after having been struck by a motor vehicle while she was walking down a highway at 2:30 AM. Toxicology studies were only positive for ethanol: vitreous ethanol 0.270 gm/dl, blood ethanol 0.238 gm/dl, urine ethanol 0.284 gm/dl. Her autopsy findings, which included but were not limited to a tear in the thoracic aorta, mediastinal hemorrhage, subgaleal hemorrhage and subarachnoid hemorrhage, were consistent with having been struck by a moving motor vehicle.

She had initiated treatment on 10 September 2003 as per p.13 of her CRF. She was last seen on []
— in treatment period [] as per page 22 of her CRF. On page 37 of her CRF, it says that the date of
her last study dose was [] and she died on []. It is unclear how it was determined
that the last dose was []

Question for Takeda: How was it determined that her last dose was [] ?

Sara E. Stradley, MS
Regulatory Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research
Phone 301-827-7430
Fax 301-443-7068

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Sara Stradley
6/1/05 12:37:19 PM
CSO

Stradley, Sara

From: Stradley, Sara
Sent: Wednesday, May 25, 2005 7:43 AM
To: 'tlynch@tgrd.com'; 'sdanielson@tgrd.com'
Cc: Stradley, Sara
Subject: info request

Tracy

Please provide a list of the studies, if any, where the effects of ramelteon on the baseline circulating levels of melatonin were evaluated.

Thanks

Sara E. Stradley, MS
Regulatory Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research
Phone 301-827-7430
Fax 301-443-7068

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Sara Stradley
5/25/05 08:00:31 AM
CSO

Stradley, Sara

From: Stradley, Sara
Sent: Tuesday, May 24, 2005 10:35 AM
To: 'tlynch@tgrd.com'; 'sdanielson@tgrd.com'
Cc: Stradley, Sara
Subject: info request

Tracy

For Study TL-025:

In study report section 10.4, on page 65 of 46629, it states that "site number 20759 did not comply with critical procedures of the study and therefore was not included in the PP population." What critical procedures were not complied with?

Thanks

Sara E. Stradley, MS
Regulatory Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research
Phone 301-827-7430
Fax 301-443-7068

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Sara Stradley
5/25/05 07:59:42 AM
CSO

Stradley, Sara

From: Stradley, Sara
Sent: Wednesday, May 11, 2005 3:12 PM
To: 'tlynch@tgrd.com'
Cc: Stradley, Sara
Subject: info request/NDA 21782

Tracy

We need the following information.

On study TL-021, Dr. [redacted], Zammit and [redacted] are listed as central scorers (protocol amendment 1).

Dr. Zammit (site # 10912) enrolled 25 patients in this protocol. Who was responsible for reviewing the PSG recording for the patients enrolled at his site?

Dr. [redacted] enrolled [redacted] patients in this protocol. Who was responsible for reviewing the PSG recording for the patients enrolled at his site?

Dr. [redacted] enrolled [redacted] patients in this protocol. Who was responsible for reviewing the PSG recording for the patients enrolled at his site?

Thanks

Sara E. Stradley, MS
Regulatory Project Manager
Division of Anesthetic, Critical Care and Addiction Drug Products
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research
Phone 301-827-7430
Fax 301-443-7068

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Sara Stradley
5/11/05 03:16:31 PM
CSO

Stradley, Sara

From: Stradley, Sara
Sent: Monday, May 09, 2005 3:12 PM
To: 'tlynch@tgrd.com'
Cc: Stradley, Sara
Subject: information request

Tracy
Regarding NDA 21-782, we need the following:

1. Study TAK-375/PFNP-002, page 95: Provide copies of references #2 and 7.
2. There appear to be inconsistencies in the narrative for subject 12815/201725 (as presented on p.5962 of Appendix D in the IAS). I have reproduced it below, underlining the areas of question. Please clarify the apparent discrepancies as well as the basis for the diagnosis of diabetes.

A 55-year-old Caucasian woman was randomized to ramelteon 16 mg. Her medical history included hypertension, headache, migraine headaches, anxiety, seasonal allergies, postmenopausal symptoms, acquired hypothyroidism, carotid bruit, intervertebral disc degeneration, gastric bypass, and "trouble with drugs in the past". Concomitant medications included BC Powder (aspirin/caffeine/salicylamide), furosemide, Synthroid (levothyroxine), conjugated estrogens, and ibuprophen. The subject's last dose of study drug was on Day 38. On Day 39 the subject was hospitalized for seizure and Type II diabetes. She presented to the emergency room with seizure, headache, nausea, and hypomagnesemia. An electroencephalogram was abnormal and showed intermittent sharp waves bilaterally. Computed tomography (CT), magnetic resonance imaging (MRI), and MR angiography scans of the head (all without contrast) were normal. Laboratory results showed glucose of 218 mg/dL; no values were reported for magnesium. Drug screens for benzodiazepines and tricyclics were positive and antidepressants were negative. She was treated with a no-caffeine, American Diabetic Association diet and given diabetic teaching. In addition to that she was treated with valproic acid, quetiapine, rofecoxib, pantoprazole, fluoxetine, pioglitazone, metformin, magnesium, potassium, and nalbuphine. On Day 33, her glucose levels were 90 mg/dL. Her condition improved and she was discharged in "fair" condition on Day 36. The discharge diagnoses were seizure disorder, migraine headaches, diffuse body aches, possible withdrawal from outpatient narcotics, and positive postictal phenomenon. The subject was withdrawn from the study due to the events. The investigator considered the events not related to study drug. These adverse events were considered treatment emergent for the integrated analysis of safety.

Sara E. Stradley, MS
Regulatory Project Manager
Division of Anesthetic, Critical Care and Addiction Drug Products
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research
Phone 301-827-7430
Fax 301-443-7068

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Sara Stradley
5/9/05 03:17:13 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

APR 18 2005

Food and Drug Administration
Rockville MD 20857

Gary K. Zammit, M.D.
Clinilabs, Inc.
1090 Amsterdam Avenue
New York, New York 10025

Dear Dr. Zammit:

Between February 3 and 9, 2005, Mr. Thomas P. Hansen, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of two clinical investigations (protocol # 01-02-TL-375-021 entitled: "A Phase III, Randomized, Double-Blind, Placebo-Controlled, PSG plus Outpatient Study to Determine the Safety and Efficacy of TAK-375 in Adults with Chronic Insomnia" and protocol # 01-02-TL-375-023 entitled: "A Phase III, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Single-Dose study of TAK-375 in Healthy Adult Volunteers in a Sleep Lab Model of Transient Insomnia") of the investigational drug [redacted] (ramelteon), performed for Takeda Global Research and Development Center, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations. We are aware that at the conclusion of the inspection, Mr. Hansen presented and discussed with you and members of your staff, Form FDA 483, Inspectional Observations. We acknowledge receipt of your response to the Form FDA 483 dated February 21, 2005. We wish to emphasize the following:

You did not maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation (21 CFR 312.62[b]).

1. According to protocol 01-02-TL-375-021, subjects must have had a Body Mass Index [BMI = weight (kg) / height (m²)] between 18 and 34 to be eligible for the study. There is inconsistent documentation of the height of subject 211426. Subject 211426 was entered into the study with a BMI of 28.32, calculated with a height of 71.5 inches and a weight of 205 pounds, recorded at screening. However, the same day, the figure 71.5 was crossed out and 61.5 entered. A height of 61.5 inches would have made the subject's BMI 38.35, and the subject would have been ineligible for the study. The case report form also indicated a height of 61.5 inches, however when this figure was questioned by the monitor 4 months later in a data clarification form, the site indicated the correct height was 71.5 inches. Other source documentation indicated the subject had a height of 69 and 72 inches. It is unclear from available study documentation what the subject's correct height was, and whether the subject was eligible for the study. We note in your response that you were unable to contact the subject to verify the correct height.

Page 2 – Gary K. Zammit, M.D.

2. For subject 231265, protocol 01-02-TL-375-023, the Body Mass Index (BMI) was incorrectly calculated. The correct BMI should have been 24.27 instead of 22.33.

We note that in your letter of February 21, 2005, you have made corrections in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies. Any response and all correspondence will be included as a permanent part of your file.

We appreciate the cooperation shown Investigator Hansen during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,



Ni A. Khin, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

Page 2 – Gary K. Zammit, M.D.

CFN/FEI:

Field Classification: VAI

Headquarters Classification:

1)NAI

2)VAI- no response required

3)VAI- response requested

4)OAI

If Headquarters classification is a different classification, explain why:

Deficiencies noted:

inadequate and inaccurate records (06)

cc:

HFA-224

HFD-170 Doc.Rm. NDA# 21-782

HFD-170 Review Div.Dir. (Rappaport)

HFD-170 MO (McNeil)

HFD-170 PM (Stradley)

HFD-46/47c/r/s/ GCP File # 11427

HFD-46/47 (Currier)

HFR-NE100 DIB (Woyschner)

HFR-NE1500 Bimo Monitor/Investigator (Hansen)

GCF-1 Seth Ray

r/d:cac: 4/13/05

reviewed:NK: 4/14/05

f/t:cac: 4/14/05

o:\cac\2005\Zammit.PDUFA.N21782.L 1 LTR.VAI.doc

Reviewer Note to Rev. Div. M.O.

The inspection of Dr. Zammit was one of 4 assignments issued to verify the data for NDA 21-782, L 1 (ramelteon). The inspection covered protocols 01-02-T1-375-021 and -023. Study records for 7 of the 25 subjects enrolled in protocol -021 and 8 of the 27 subjects in protocol -023 were examined during the inspection. Records examined included source documents, CRFS, labs, PSG calculations, drug accountability records, and correspondence with the sponsor and IRB. A comparison was made between the efficacy variable values collected by the site and central reader, with those recorded on CRFs and those provided in efficacy line listings from the sponsor.

Two record-keeping errors were noted during the inspection, both involving the calculation of the BMI for subjects. For subject 211246, protocol -021, source documents exist indicating the

subject was 61.5 inches tall and 71.5 inches tall. If the subject was 61.5 inches tall, the BMI (38.35) would fall outside the protocol limit (18 - 34) and the subject would have been ineligible for the study.

The inspection included a check of the primary and secondary efficacy variables (LPS and # of awakenings taken from PSG readings) for subjects in protocol -021. The values were calculated on-site using Appendix H of the protocol by FDA field investigator Hansen; Dr. Zammit, principal investigator; L

J Discrepancies were found in the data for three

subjects:

SUBJECT	DAY	MEASUREMENT	VALUE REPORTED ON LINE LISTINGS	VALUE CALCULATED ON SITE
211029	20-Mar-2003	LPS	44	58.5
211030	24-Mar-2003	# of awakenings	16	12/21
211030	05-May-2003	# of awakenings	19	16
211028	16-Mar-2003	# of awakenings	5	25
211028	17-Mar-2003	# of awakenings	3	23/22
211028	27-Apr-2003	# of awakenings	4	20*
211028	28-Apr-2003	# of awakenings	3	16*

More than one value in the last column indicates differing calculations by persons on site. Those marked by an * indicated values calculated solely by FDA investigator Hansen

While it is common to find slightly different calculations obtained from PSG readings made by different readers, some of the above differences are significant. It should be noted that in all cases except one, the values reported by the sponsor in the line listings favored a more positive efficacy conclusion.

In general, Dr. Zammit's study was conducted appropriately without significant deviations. With the *possible* exception of subject 211246 in protocol -021, all subjects whose data was reviewed were eligible for the study. With the *possible* exception of the efficacy endpoints for the 3 subjects noted in the above chart for protocol -021, study data was reported accurately. With these caveats, the data from Dr. Zammit's studies could be used to support an approval decision.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Ni Aye Khin
4/22/05 12:11:10 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

APR 18 2005

Curtis D. Kauffmann, M.D.
Harmony Research, Inc.
3312 Wayfield Drive
Johnson city, Tennessee 37601

Dear Dr. Kauffman:

Between February 28 and March 3, 2005, Mr. Edward H. Maticka, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol # 01-02-TL-375-025 entitled: "A Phase III, Randomized, Double-Blind, Placebo-Controlled, Outpatient Safety and Efficacy Study of TAK-375 in Elderly Subjects with Chronic Insomnia" of the investigational drug [redacted] (ramelteon), performed for Takeda Global Research and Development, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations. We note that Mr. Maticka discussed findings with you and Ms. Katherine Kauffmann, your Research Administrator, at the conclusion of the inspection. We wish to emphasize the following:

You did not maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation (21 CFR 312.62[b]).

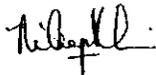
1. There was a discrepancy between data recorded on source documentation and data reported on case report forms (CRFs.) Specifically, the source document recording the results of a GI body system exam for subject 252256 was blank, whereas the CRF indicated the results were normal, and the source document for subject 252470 recording the results of body system exams for the extremities, musculoskeletal, and nervous systems was blank, whereas the CRF indicated the exams were normal.
2. The study screening log indicated subject 252030 was screened and administered drug on Day 1. Subject records do not indicate any drug was given and drug accountability records do not reflect any study drug administered.
3. One of six study drug blinding labels was missing in the study records for subject 252470.

Please make appropriate corrections in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies.

Page 2 - Curtis D. Kauffmann

We appreciate the cooperation shown Investigator Maticka during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,



Ni A. Khin, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

Page 3 – Curtis D. Kauffmann

CFN/FEI:

Field Classification:NAI

Headquarters Classification:

_____ 1)NAI

2)VAI- no response required

_____ 3)VAI- response requested

_____ 4)OAI

If Headquarters classification is a different classification, explain why: Noted discussion items were record keeping issues to be mentioned in a letter.

Deficiencies noted:

inadequate and inaccurate records (06)

cc:

HFA-224

HFD-170 Doc.Rm. NDA#21-782

HFD-170 Review Div.Dir. (Rappaport)

HFD-170 MO (McNeil)

HFD-170 PM (Stradley)

HFD-46/47c/r/s/ GCP File # 11473

HFD-46/47 (Currier)

HFR-SE340 (Lewis) DIB

HFR-SE350 (Abel) Bimo Monitor

HFR-SE3545 (Maticka) Field Investigator

GCF-1 Seth Ray

r/d:cac:n 4/12/05

reviewed:NK: 4/12/05

f/t:cac:

o:\cac\2005\Kauffmann.PDUFA.N21782.L }VAI.doc

Reviewer Note to Rev. Div. M.O.

The inspection of Dr. Kauffmann was 1 of 4 assignments issued to verify data from NDA 21-782, [] Dr. Kauffmann screened 39 subjects and enrolled 28. Study records for 9 of the 28 subjects were examined during the inspection. The enrolled subjects were not Dr. Kauffmann's private patients, so medical histories were sparse. Third-party medical history was present for 5 of the 9 subjects reviewed. Study records examined included informed consents, source documents, CRFs, queries from the CRO, lab reports, study diaries, ECGs, general correspondence with the IRB and sponsor, drug accountability records, and advertising. Data listings provided as background material (from the sponsor) were compared to source documents for protocol adherence (I/E criteria, dosing, etc), subject sleep data recorded in subject diaries, and termination/discontinuation data. No discrepancies were noted between source documents

and data listings. Source documents also generally agreed with CRFs. Informed consents were present for all 28 subjects. No Form FDA 483 was issued, however several items were discussed with Dr. and Mrs. Kauffmann (Research Administrator) at closeout:

1. The protocol stated that a randomization schedule would be generated and subjects would be assigned sequential drug kits in the order they enrolled. However, the sponsor did not send the drug kits in sequential order, so Dr. Kauffmann assigned the kits he received to the subjects as they enrolled. All subjects were randomly enrolled and the site was blinded to the randomization. This was the sponsor's problem, not the investigator's.
2. For 2 subjects, boxes indicating "normal" exams of body systems (subject 252556 – GI system, and subject 252470 - extremities, musculoskeletal, and nervous systems) were left blank on source documents but marked normal on CRFs.
3. The BWSQ symptoms CRF had a space for the subject to initial the form. In 4 instances it appeared the initials were not the same as those on the pages of the informed consent document. There was no protocol requirement for subjects to sign the BWSQ form. Without a handwriting expert, it cannot definitely be said the initials were not those of the subjects.
4. Each subject should have had 6 blinding labels in their study files. Subject 252470 only had 5 (1 missing).
5. It was unclear what advertising was used for the study and whether it was approved by the IRB. Copies of a poster and video were eventually found (the poster had been approved, the video had not but contained the same generic information as the poster). Dr. Kauffmann had thought there was newspaper advertising, but no copies could be found nor was there any reference in any subject chart about being recruited through a newspaper ad.
6. The study screening log indicated subject 252030 (screened but not enrolled) received drug on day 1, however there was no randomization code, no record of drug dispensed, and the subject's file did not indicate any drug given. It appears the entry on the screening log was an error.
7. Normal office procedure for signatures on source documents was that the person entering the data signed, and Dr. Kauffman added notations about subject's eligibility to remain in the study. A few source forms did not have Dr. Kauffmann's notations. Notations by the PI were not required by the protocol. The field investigator discussed the need for consistent GCP record keeping practices.

All of the discussed items appear to be minor. Items 2, 4, and 6 appear to be record-keeping errors, and although we are citing the investigator for not keeping accurate records, the errors appear to have had little or no impact on subject safety. The only possible exception is that it cannot be confirmed that 2 subjects had all body systems examined at screening. None of the errors would appear to impact on efficacy results for the study.

From the records examined, it appears the data from Dr. Kauffman's study could be used to support an approval decision for ND 21-782.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Ni Aye Khin
4/22/05 12:07:43 PM

Stradley, Sara

From: Stradley, Sara
Sent: Thursday, March 31, 2005 9:50 AM
To: 'tlynch@tgrd.com'
Cc: Stradley, Sara
Subject: information request

Tracy
Below is another information request for NDA 21-782.

The request refers to Study 01-02-TL-375-021. This request mimics our previous request for Study 01-02-TL-375-025.

The application states:

The SAP for this study was amended to reflect problems with data collection that were discovered during the study. The protocol specified that the data for study weeks would be classified into visits using specified "windows" of the study days: "Weekly time windows will be defined (i.e. Nights 1-7, 8-14, 15-21, 22-28, 29- last dose of double-blind study medication). The average of the nonmissing data for a weekly time window will be analyzed." Because the dates recorded on the diary CRFs were deemed to be potentially inaccurate, the data recorded on the CRFs were applied to the visit label on the CRF. No recorded dates were checked. With diaries being returned to the clinics on Days 15, 29, and 36, the appropriate labels for the diary data during treatment are: "Weeks 1-2," "Weeks 3-4", and "Week 5". The final SAP for the study, as completed prior to unblinding, included these changes.

Provide a table identifying and enumerating the patients that dropped out during each week. A drop-out should be calculated based on the day following the last dose of medication received.

Thanks

Sara E. Stradley, MS
Regulatory Project Manager
Division of Anesthetic, Critical Care and Addiction Drug Products
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research
Phone 301-827-7430
Fax 301-443-7068

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Sara Stradley
3/31/05 09:53:54 AM
CSO

Stradley, Sara

From: Culley, Kimberly
Sent: Tuesday, March 22, 2005 7:54 AM
To: Stradley, Sara
Subject: FW: clarification

Hi Sara,

Appears that the "professional sample" is the only change to the labeling we previously reviewed (DMETS consult # 05-0010, signed off March 2005). I would like to say that we do not feel a [] sample is a good idea (fear of overdose, adverse reactions, lack of effect, etc).

So at this time, we do not have anything further to review, so I will close up this review request.

Thanks so much for your help and call if you need anything!
kim

-----Original Message-----

From: tlynch@tgrd.com [mailto:tlynch@tgrd.com]
Sent: Monday, March 21, 2005 9:08 AM
To: CulleyK@cder.fda.gov
Subject: RE: clarification

Good Morning Kimberly,

The [] bottle label was re-submitted with the "professional sample" tag to be used as a sample package, in addition to the 3-count sample box. You are correct, due to the lead time for the production of the 3-tab sample package, and our absence of a trade name, we decided to use the [] bottle as a professional sample for a short duration. The label and package configuration is identical, except for the "professional sample" tag.

Please let me know if I have clarified our intent.

Thank you,

Tracy

-----Original Message-----

From: Culley, Kimberly [mailto:CulleyK@cder.fda.gov]
Sent: Friday, March 18, 2005 12:54 PM
To: Stradley, Sara; Lynch, Tracy (TGRD)
Subject: RE: clarification

Hi Tracy,

I apologize for my confusion, but I still have questions. I suppose the basic question is why the [] bottle was relabeled with the "professional sample" tag? Do you expect to have difficulty with production of the previously submitted 3-tab sample box?

Depending on your answer- these questions may prove irrelevant. The labeling as submitted is identical to the previously submitted [] bottle other than the "professional sample" statement. Are you planning to market a [] sample? Or did you intend for the [] to be changed to another number?

3/22/2005

I suppose I should start there....then follow-up after you respond. Your first response will probably clear up my confusion!

Thanks so much,
kim

*Kimberly Culley, Safety Evaluator
Office of Drug Safety
Division of Medication Errors & Technical Support
Food & Drug Administration
Phone: 301-827-6277
Fax: 301-443-9664
E-mail: culleyk@cder.fda.gov*

-----Original Message-----

From: Stradley, Sara
Sent: Friday, March 18, 2005 12:56 PM
To: 'tlynch@tgrd.com'; Stradley, Sara; Culley, Kimberly
Subject: RE: clarification

Tracy

Kim Culley from DMETS has some additional questions regarding this sample package. I have include her in the email so that she can direct any questions to you.

Sara

-----Original Message-----

From: tlynch@tgrd.com [mailto:tlynch@tgrd.com]
Sent: Friday, March 18, 2005 11:49 AM
To: STRADLEYS@cder.fda.gov
Subject: RE: clarification

Hi Sara,

The [] sample package was in addition to the 3 count sample package originally submitted. The alternate sample package was submitted due to the rejection of our proposed trade names and the lead time for production. The [] bottle was already submitted in the NDA with stability, therefore the only change to the original label was the identification as a 'sample'. Both packaging configurations are presented for approval.

Kindest Regards,

Tracy

-----Original Message-----

From: Stradley, Sara [mailto:STRADLEYS@cder.fda.gov]
Sent: Friday, March 18, 2005 10:07 AM
To: Lynch, Tracy (TGRD); Stradley, Sara
Subject: clarification

Tracy

Could you clarify an issue regarding the [] sample package that was sent Feb 22, 2005.

<<...OLE_Obj...>>

Have you changed from a 3 tablet professional sample []

Sara E. Stradley, MS
Regulatory Project Manager
Division of Anesthetic, Critical Care and Addiction Drug Products
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research
Phone 301-827-7430
Fax 301-443-7068

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Sara Stradley
3/22/05 08:22:57 AM
CSO

Stradley, Sara

From: Stradley, Sara
Sent: Tuesday, March 15, 2005 1:59 PM
To: Stradley, Sara; 'tlynch@tgrd.com'
Subject: RE: info request

Tracy
The request refers to Study 01-02-TL-375-025

Sara

-----Original Message-----

From: Stradley, Sara
Sent: Tuesday, March 15, 2005 1:57 PM
To: 'tlynch@tgrd.com'
Cc: Stradley, Sara
Subject: info request

Tracy
We need the following information

NDA 21782 states:

The planned analyses for this study as specified in the protocol were amended to reflect problems with data collection that were discovered during the study. The protocol specified that the data for study weeks would be classified into visits using specified "windows" of the study days: "Weekly time windows will be defined (i.e. Nights 1-7, 8-14, 15-21, 22-28, 29- last dose of double-blind study medication). Because the dates recorded on the diary CRFs were deemed to be potentially inaccurate, the data recorded on the CRFs were applied to the visit label on the CRF. For example, all data recorded on the CRF for Week 1 were analyzed for that visit. No recorded dates were checked. THE SAP was finalized for the study, prior to unblinding, included these changes."

As a result, some patients have more than 7 days of assessments for some weeks (example PATID 251043). This presents difficulty when attempting to ascertain the number of patients that dropped out per week. **Provide a table identifying and enumerating the patients that dropped out during each week. A drop-out should be calculated based on the day following the last dose of medication received.**

Sara E. Stradley, MS
Regulatory Project Manager
Division of Anesthetic, Critical Care and Addiction Drug Products
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research
Phone 301-827-7430
Fax 301-443-7068

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Sara Stradley
3/15/05 02:00:48 PM
CSO

Stradley, Sara

From: Stradley, Sara
Sent: Wednesday, February 16, 2005 4:07 PM
To: 'tlynch@tgrd.com'
Cc: Stradley, Sara
Subject: info needed

Tracy

Please provide us with the historical control data of spontaneous tumor incidence in control B6C3F1 mice and Sprague-Dawley rats as found by [] (the contract lab conducting the Ramelteon carcinogenicity studies) from 2-year bioassays around the years that the studies were ongoing (i.e. 1999-2001). We need this information as soon as to evaluate your carcinogenicity data.

Let me know if you need any clarification.

Sara E. Stradley, MS
Regulatory Project Manager
Division of Anesthetic, Critical Care and Addiction Drug Products
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research
Phone 301-827-7430
Fax 301-443-7068

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Sara Stradley
2/16/05 04:32:50 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

3/7/05

NDA 21-782

INFORMATION REQUEST LETTER

Takeda Global Research & Development Center, Inc.
475 Half Day Road
Lincolnshire, IL 60069

Attention: Steve Danielson
Manager, Regulatory Affairs

Dear Mr. Danielson:

Please refer to your September 21, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ramelteon 8 mg.

We acknowledge your January 7, 2005 submission which contained a request for the tradename review of [redacted]

Your submission dated February 4, 2005, which contains revised labeling based on your response to our December 17, 2005 letter, is still under review.

The Division of Medication Errors and Technical Support (DMETS) has reviewed the January 7, 2005 submission and has the following comments and information requests in addition to the comments listed in the December 17, 2005 letter. We request a prompt written response in order to continue our evaluation of your NDA.

TRADENAME

1. The proposed tradename, [redacted] is not acceptable due to orthographic similarity and overlapping product characteristics with Boniva.
2. The proposed tradename, [redacted] is not acceptable based on promotional concerns.

GENERAL COMMENT

Include the dosage form in conjunction with the established name on the blister label, carton and shipper carton of the professional samples.

SHIPPER CARTON and CARTON (Professional Sample)

Relocate [redacted] from the proprietary name as it could be confused as the letters [redacted]

CONTAINER LABEL (30's, 100's and 500's)

1. Please ensure the established name is at least ½ the size of the proprietary name as per 21 CFR 201.10 (g)(2).
2. De-bold and relocate the net quantity away from the proprietary name. The current presentation has increased prominence and appears directly above the proprietary name. This may result in confusion with the product strength.
3. Ensure that child resistant closures are used for bottles intended for unit-of-use to be in accordance with the Poison Prevention Act.

If you have any questions, call Sara E. Stradley, Regulatory Project Manager, at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief Project Manager
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Parinda Jani
3/7/05 01:56:41 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

12/17/04
Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-782

INFORMATION REQUEST LETTER

Takeda Global Research & Development Center, Inc.
475 Half Day Road
Lincolnshire, IL 60069

Attention: Steve Danielson
Manager, Regulatory Affairs

Dear Mr. Danielson:

Please refer to your September 21, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ramelteon 8 mg.

The Division of Medication Errors and Technical Support (DMETS) has reviewed the referenced materials and has the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

TRADENAME

The proposed tradename, [] is not acceptable due to the potential confusion with the recently approved drug, Lunesta. The drug products share overlapping characteristics of dosage, route administration, indication of use, dosage regimen, patient and prescriber populations, and potential proximity on the pharmacy shelves.

BLISTER LABEL (3 tablet Professional Sample)

1. Revise to read 8 mg/tablet on the top part of the blister card.
2. Revise to read "tablet" rather than "tablets" on each individual blister cell.
3. Revise the placement of the lot number and expiration date to appear at the bottom of the label subsequent to the drug name and strength.
4. Delete the [] that appears on each blister. This obscures the readability of the text.
5. Relocate the statement "Professional Sample- Not for Sale" to the principal display panel.

CARTON (Professional Sample)

No comment at this time.

SHIPPER CARTON (6 Professional Sample Units)

1. Ensure that the established name is at least ½ the size of the proprietary name as per the requirements of 21 CFR 201.10 (g) (2).
2. Increase the prominence of the product strength to aid in proper identification and differentiation.

CONTAINER LABEL (30's, 100's and 500's)

1. Relocate the net quantity statement away from the product strength. The current presentation has increased prominence and may result in confusion with the product strength.
2. Ensure that child resistant closures are used for bottles intended to be a "unit of use" (e.g. 30 tablets) to be in accordance with the Poison Prevention Act.
3. The current [] used to highlight the proprietary name makes this name difficult to discern. Revise accordingly.

PACKAGE INSERT (INFORMATION FOR THE PATIENT)

Consider the addition of a warning about the concomitant use of alcohol and fluvoxamine with ramelteon. This information will assist a patient and practitioner to the proper drug usage.

If you have any questions, call Sara E. Stradley, Regulatory Project Manager, at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief Project Manager
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Parinda Jani

12/17/04 03:03:54 PM

12/13/04

NDA REGULATORY FILING REVIEW (Including Memo of Filing Meeting)

NDA # 21-782 Supplement # SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8

Trade Name:
Generic Name: ramelteon
Strengths: 8 mg

Applicant: Takeda Global Research & Development Center, Inc.

Date of Application: September 21, 2004
Date of Receipt: September 22, 2004
Date clock started after UN: -----
Date of Filing Meeting: November 10, 2004
Filing Date: November 21, 2004
Action Goal Date (optional): July 22, 2005 User Fee Goal Date: July 22, 2005

Indication(s) requested: treatment of insomnia

Type of Original NDA: (b)(1) X (b)(2) _____
OR
Type of Supplement: (b)(1) _____ (b)(2) _____

NOTE:

- (1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.
- (2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:
_____ NDA is a (b)(1) application OR _____ NDA is a (b)(2) application

Therapeutic Classification: S X P _____
Resubmission after withdrawal? _____ Resubmission after refuse to file? _____
Chemical Classification: (1,2,3 etc.) 1
Other (orphan, OTC, etc.) _____

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee Status: Paid X Exempt (orphan, government) _____
Waived (e.g., small business, public health) _____

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx to OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling.

If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES NO

If yes, explain:

- Does another drug have orphan drug exclusivity for the same indication? YES NO

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES N/A NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain.

- If yes, has OC/DMPQ been notified of the submission? YES N/A NO

- Does the submission contain an accurate comprehensive index? YES NO

- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES NO

If no, explain:

They had to send in the appropriate wording for the debarment certification.

- If an electronic NDA, does it follow the Guidance? N/A YES NO
If an electronic NDA, all certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format?

All electronic except for the required paper copies.

- If in Common Technical Document format, does it follow the guidance? N/A YES NO

It is an electronic NDA in CTD format.

- Is it an electronic CTD? N/A YES NO
If an electronic CTD, all certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format?

Additional comments: None

- Patent information submitted on form FDA 3542a? YES NO
- Exclusivity requested? YES, NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

They requested exclusivity but did not mention the timeframe. It should be 5 yrs since it is an NME.

- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

They had to send the resend the debarment certification with the correct language.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge"

- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)
- Field Copy Certification (that it is a true copy of the CMC technical section)? YES NO

1.3.2 Field Copy Certification

A paper field copy of this NDA will not be submitted to the district office as this submission will be electronically submitted to the agency. In accordance with the guidance provided by the division at the pre-NIDA Type B meeting for ramelteon held with the agency on June 22, 2004, Takeda Global Research & Development Center, Inc. will provide a letter to the home district office certifying that the electronic NDA has been submitted to CDER FDA project manager.

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? YES NO
 If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name/Applicant name correct in COMIS? YES NO
 If not, have the Document Room make the corrections.
- List referenced IND numbers: IND 58,136
- End-of-Phase 2 Meeting(s)? Date(s) November 8, 2001 NO
 If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) June 22, 2004 (clinical) NO
December 15, 2003 (CMC)

If yes, distribute minutes before filing meeting. All are in DFS and available to the reviewers.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES NO
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? YES NO
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A YES NO
- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
 If no, did applicant submit a complete environmental assessment? YES NO
 If EA submitted, consulted to Florian Zielinski (HFD-357)? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES NO

Appears This Way
 On Original

ATTACHMENT

MEMO OF FILING MEETING

DATE: November 10, 2004

BACKGROUND: The Sponsor requested a priority review. However the Division (see email at end of this memo) decided that it did not qualify for the priority review.

ATTENDEES: Rob Shibuya, Rigoberto Roca, Dionne Price, Tom Permutt, Adam Wasserman, Dan Mellon
 Pat Maturu, Suresh Doddapaneni, Bob Rappaport, D. Elizabeth McNeil

ASSIGNED REVIEWERS:

<u>Discipline</u>	<u>Reviewer</u>
Medical:	Rob Shibuya, Team Leader Rigoberto Roca
Secondary Medical:	----
Statistical:	Dionne Price, Team Leader Tom Permutt
Pharmacology:	Adam Wasserman, Supervisor Dan Mellon
Statistical Pharmacology:	----
Chemistry:	Pat Maturu, Team Leader Ravi Harapanhalli
Environmental Assessment (if needed):	----
Biopharmaceutical:	David Lee, Team Leader Suresh Doddapaneni
Microbiology, sterility:	----
Microbiology, clinical (for antimicrobial products only):	----
DSI:	----
Regulatory Project Management:	Sara Stradley
Other Consults:	CSS/ODS/DDMAC

Per reviewers, are all parts in English or English translation? YES NO
 If no, explain:

CLINICAL	FILE <u>X</u>	REFUSE TO FILE _____
• Clinical site inspection needed:	<u>TBD</u>	YES NO
• Advisory Committee Meeting needed?	YES, date if known _____	<u>NO</u>
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?	<u>N/A</u>	YES NO

CLINICAL MICROBIOLOGY	NA <u>X</u>	FILE _____	REFUSE TO FILE _____
STATISTICS		FILE <u>X</u>	REFUSE TO FILE _____
BIOPHARMACEUTICS		FILE <u>X</u>	REFUSE TO FILE _____

	• Biopharm. inspection needed:	<u>TBD</u>	YES	NO
PHARMACOLOGY	NA _____	FILE <u>X</u>	REFUSE TO FILE _____	
	• GLP inspection needed:	<u>TBD</u>	YES	NO
CHEMISTRY		FILE <u>X</u>	REFUSE TO FILE _____	
	• Establishment(s) ready for inspection?		<u>YES</u>	NO
	• Microbiology	<u>TBD</u>	YES	NO
CSS		FILE <u>X</u>	REFUSE TO FILE _____	

ELECTRONIC SUBMISSION:

Any comments: Pharm/Tox stated that the links were very "lose". They also requested a revised Table of Contents with study titles included and a missing in vitro genotoxicity study. All of these comments were relayed to the sponsor on Nov 12, 2004. The Sponsor provided an updated Table of Contents and provided the missing genotoxic study. The linkage problems were resolved by updating the Abode settings on the reviewer's computer.

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

X_____ The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

_____ No filing issues have been identified.

X_____ Filing issues to be communicated by Day 74. List (optional):

Drug Substance

1. The CMC data from your IND 58,136 indicates that the [] is made from [] The current acceptance specifications for [] need to be tightened. Provide data on characterization and tighter specifications for the assay and impurities.
2. Provide a description of how you oversee the [] at your contract manufacturer's site.
3. Tighten the acceptance criteria for the related substances and provide statistical basis for the justification.

Drug Product

4. Provide data on [] for the developmental and registration batches and include them as [] in the manufacture of the drug product.
5. Tighten the specification for [] in the drug product and provide statistical basis for the justification.
6. Provide updated stability report with statistical analysis for the site specific batches manufactured at Takeda Ireland. Note that the stability updates may be submitted within the last three months before the review clock for our consideration.

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of the RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. Document filing issues/no filing issues conveyed to applicant by Day 74.

Regulatory Project Manager, HFD-170

Email Regarding Priority versus Standard Review

-----Original Message-----

From: McNeil, D Elizabeth
Sent: Monday, October 18, 2004 5:06 PM
To: Roca, Rigoberto A; Doddapaneni, Suresh; Permutt, Thomas J; Price, Dionne; Maturu, Pramoda K; Mellon, Dan; Wasserman, Adam
Cc: McNeil, D Elizabeth; Rappaport, Bob A
Subject: Clinical comments on priority review, feel free to chime in

Clinical comments on the request for priority review of ramelteon:

I recommend that this product not be granted a priority review. MaPP 6020.3 provides for priority review of new drugs that "if approved, would be a *significant improvement compared to marketed products*...in the treatment, diagnosis or prevention of a disease (*emphasis added*)" The improvement may be manifest as the "elimination or a substantial reduction of a *treatment limiting drug reaction*... (*emphasis added*)"

Ramelteon, a selective MT₁ and MT₂ receptor agonist, neither prevents insomnia nor affects diagnosis of insomnia. The only possible reason for priority consideration would be demonstration of improved insomnia treatment. The sponsor proposed that ramelteon be granted a priority review due to the potential for "elimination or reduction of a treatment limiting drug reaction." The two major factors, as stated on page 4/22 of their rationale, for their proposal are 1) the medical and economic consequences of insomnia in the US that establish it as a public health burden and 2) the unmet need for safe effective treatment of insomnia without the deleterious side effects of the benzodiazepines, other BZRAs and sedating antidepressants.

Insomnia may be an undertreated and underdiagnosed condition, however, the mere fact that a condition contributes to the public health burden does not require that drugs purporting to treat that condition should all receive priority review. In order to receive a priority review, a product should represent a *significant improvement compared to marketed products*. The sponsor claims that ramelteon has no potential for abuse, does not cause dependence, is not associated with withdrawal effects, does not cause rebound insomnia, and does not exhibit residual pharmacologic effects (p.4/22 of the provided rationale).

The potential for abuse and the issue of physical dependence do not represent *treatment limiting drug reactions*.

The limited rebound insomnia reported with the BZRAs does not represent a *treatment limiting drug reaction*.

The transient decrement in alertness seen after use of hypnotics, "so-called traveler's amnesia" does not represent a *treatment limiting drug reaction* but rather speaks to the need for use of good clinical judgment and the importance of patient education in prescribing.

While there may be treatment limiting drug reactions to the benzodiazepines in the elderly, the sponsor has not provided adequate data to support that these types of drug reactions exist with use of the BZRA in this population.

While review of the submitted data may reveal that ramelteon, with its novel mechanism of action, represents a beneficial addition to the available armamentarium of hypnotics, the rationale provided does not support the sponsor's claim that ramelteon provides a substantial improvement as compared to currently approved marketed products, specifically zaleplon and zolpidem.

Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

**Appears This Way
On Original**

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES NO

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

YES NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," skip to question 4. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)?

YES NO

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

4. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," skip to question 5. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

NOTE: If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, YES NO
ORP?

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES NO

If "No," skip to question 6.

If "Yes," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.

- (b) Is the approved drug product cited as the listed drug? YES NO

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES NO

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES NO

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES NO

10. Are there certifications for each of the patents listed for the listed drug(s)? YES NO

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)

*IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

21 CFR 314.50(i)(1)(ii): No relevant patents.

21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?

YES NO

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

N/A YES NO

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

N/A YES NO

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

YES NO

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

YES NO

- EITHER
 The number of the applicant's IND under which the studies essential to approval were conducted.

IND # _____ NO

 OR
 A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

YES NO

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES NO

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Sara Stradley
12/13/04 09:35:30 AM
CSO

12/10/04

Office of Drug Safety

MEMO

To: Bob Rappaport, M.D.
Director, Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170

From: Kim Culley, RPh
Safety Evaluator, Division of Medication Errors and Technical Support
Office of Drug Safety, HFD-420

Through: Alina Mahmud, RPh, Team Leader
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support
Office of Drug Safety, HFD-420

CC: Sara Stradley
Project Manager, Division of Anesthetic, Critical Care, and Addiction Drug Products,
HFD-170

Date: November 19, 2004

Re: ODS Consult 03-0251-1 [] (Ramelteon) Tablets; NDA 21-782

NOTE: This review contains proprietary and confidential information that should not be released to the public.

This memorandum is in response to a September 22, 2004 request from your Division for a label and labeling review of the proprietary name, [] The proprietary name of [] was reviewed by DMETS on January 14, 2004 and found to be acceptable. However since this review, the proprietary name Lunesta^{***} has been identified as a name that may lead to confusion with the proposed name []

I. LOOK-ALIKE NAME

[] may look similar to Lunesta^{***} when scripted. Lunesta^{***} is a name recently reviewed by DMETS (Consult number 04-0284, NDA# 21-476). Lunesta^{***} contains eszopiclone that is a nonbenzodiazepine indicated for the treatment of insomnia characterized by difficulty falling asleep, and/or difficulty maintaining sleep during the night and early morning. The drug product is available as 1 mg, 2 mg and

^{***} Proprietary and confidential information that should not be released to the public.

3 mg tablets. Proposed dosing is 2 mg immediately before bedtime for nonelderly adults whose primary complaint is difficulty falling asleep with 3 mg immediately before bedtime for patients with difficulty staying asleep. In elderly patients, both the 1 mg and 2 mg decrease sleep latency, and 2 mg is effective for sleep maintenance. The look-alike similarities stem from the identical leading "Lun" compounded by the likeness of succeeding "i" and "e" and the shared concluding "a" (see page 7)

Lunesta /

The drug products share the overlapping characteristics of dosage form (tablet), route administration (oral), indication of use (insomnia), dosage regimen (one tablet at bedtime), patient and prescriber populations, and potential proximity on the pharmacy shelves due to the identical leading three letters. This shared leading "Lun" may also lead to computer order entry errors. Confusion between the names and computer order entry errors may be compounded by the potential for the 3 mg strength of Lunesta[™] to be misinterpreted as 8 mg (of [] since the numbers 3 and 8 can look similar when scripted. DMETS has no objections to the use of the proprietary name [], provided that only one name [] (NDA 21-782) or Lunesta[™] (NDA 21-476) is approved. There is a high potential for name confusion especially if both products are introduced into the marketplace in close proximity to each other. The PDUFA date for [] is July 22, 2005 and the PDUFA date for Lunesta[™] is December 15, 2004. The acceptability of the proposed proprietary name [] depends on which application, [] or Lunesta[™], receives approval first, as these two names may not co-exist due to their similar name and product characteristics.

II. LABEL AND LABELING

In review of the [] container label, carton and insert labeling, DMETS has attempted to focus on safety issues relating to possible medication errors and have identified the following areas of possible improvement.

A. BLISTER LABEL (3 tablet Professional Sample)

1. Revise to read 8 mg/tablet on the top part of the blister card.
2. Revise to read "tablet" rather than "tablets" on each individual blister cell.
3. Revise the placement of the lot number and expiration date to appear at the bottom of the label subsequent to the drug name and strength.
4. Delete the [] that appears on each blister. This obscures the readability of the text.
5. Relocate the statement "Professional Sample- Not for Sale" to the principal display panel.

B. CARTON (Professional Sample)

No comment at this time.

C. SHIPPER CARTON (6 Professional Sample Units)

1. Please ensure that the established name is at least ½ the size of the proprietary name as per 21 CFR 201.10 (g) (2).

[™] Proprietary and confidential information that should not be released to the public.

2. Increase the prominence of the product strength to aid in proper identification and differentiation.

D. CONTAINER LABEL (30's, 100's and 500's)

1. Relocate the net quantity statement away from the product strength. The current presentation has increased prominence and may result in confusion with the product strength.
2. Ensure that child resistant closures are used for bottles intended to be a "unit of use" (e.g. 30 tablets) to be in accordance with the Poison Prevention Act.
3. The current [] used to highlight the proprietary name makes this name difficult to discern. Revise accordingly.

E. PACKAGE INSERT (INFORMATION FOR THE PATIENT)

Please consider the addition of a warning about the concomitant use of alcohol and fluvoxamine with [] This information will assist a patient and practitioner to the proper drug usage.

In summary, due to the similarity in name and product characteristics between [] and Lunesta[™], we believe that the products may not coexist in the marketplace. There is a high potential for name confusion especially if both products are introduced into the marketplace in close proximity to each other. The PDUFA date for [] is July 22, 2005 and the PDUFA date for Lunesta[™] is December 15, 2004. The acceptability of the proposed proprietary name [] depends on which application, [] or Lunesta[™], receives approval first, as these two names may not co-exist due to their similarities. DMETS also recommends implementation of the label and labeling revisions outlined in this memo that may lead to safer use of the product. If you have any questions or need clarification, please contact Sammie Beam, Project Manager, at 301-827-2102.

**Appears This Way
On Original**

[™] Proprietary and confidential information that should not be released to the public.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Kimberly Culley
12/10/04 03:12:14 PM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
12/10/04 03:23:09 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
12/10/04 03:39:23 PM
DRUG SAFETY OFFICE REVIEWER

12 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

11/30/04



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-782

Takeda Global Research & Development Center, Inc.
475 Half Day Road
Lincolnshire, Illinois 60069

Attention: Steve Danielson
Manager, Regulatory Affairs

Dear Mr. Danielson:

Please refer to your September 21, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for [] (ramelteon) Tablet, 8mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on November 21, 2004, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues. If the requested data is submitted in the NDA you may reference the location of the data within the NDA. If not, provide the requested data at an earliest date to facilitate the review process.

Drug Substance

1. The CMC data from your IND 58,136 indicates that the [] is made [] The current acceptance specifications for [] need to be tightened. Provide data on characterization and tighter specifications for the assay and impurities.
2. Provide a description of how you oversee the synthesis of [] at your contract manufacturer's site.
3. Tighten the acceptance criteria for [] and provide statistical basis for the justification.

Drug Product

4. Provide data on [] for the [] developmental and registration batches and include them [] in the manufacture of the drug product.

5. Tighten the specification for ζ in the drug product and provide statistical basis for the justification.
6. Provide updated stability report with statistical analysis for the site specific batches manufactured at Takeda Ireland. Note that the stability updates may be submitted within the last three months before the review clock for our consideration.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

If you have any questions, call Sara Stradley, Regulatory Project Manager, at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Bob Rappaport, MD
Division Director
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Bob Rappaport
11/30/04 11:56:37 AM

Stradley, Sara

From: sdanielson@tgrd.com
Sent: Tuesday, November 16, 2004 1:21 PM
To: stradleys@cder.fda.gov
Cc: tlynch@tgrd.com; bphillips@tgrd.com; pnoblin@tgrd.com
Subject: Ramelteon NDA 21-782 - sponsor response in inquiry
Importance: High

Hi, Sarah,

I've interpolated our responses within your original email below. Please let me know if we need to clarify anything.

Best regards,

Steve

Steve

We need the following issues addressed. We have had some trouble navigating the electronic submission and it appears the links need to be tightened. The missing study needs to be submitted prior to the filing date of Nov 21, 2004.

Sara

1) Table of contents request: In the Pharmtoc.pdf (Pharmtox Table of Contents) it would be significantly more useful if the Description column contained the study titles or at least an abbreviated description of the content of the study instead of being identified by study number. The column titled "Review copy volume location number" is unused and not necessary and could contain the study number/designation. Using the methodology of the following example for your table of contents would greatly aid review:

Description/Study Title	Study #	Archive copy location folder/file name
4.2.1 Pharmacology		
4.2.1.1 Primary Pharmacodynamics		
Effects of TAK-375 on melatonin receptors	M-11-00617	pharmtox\pharm\m-11-00617.pdf
Effects of TAK-375 and metabolite M-II on human MT ₂ receptor	M-11-00616.001	pharmtox\pharm\m-11-00616001r.pdf

[Danielson, Steven (TGRD)] *The table of content format is consistent with the "Guidance for Industry: Providing Regulatory Submissions in Electronic Format - NDAs" (January 1999) (cf p24, item 2, and the example ToC provided in this FDA link: http://www.fda.gov/cder/guidance/NDA_Example.htm) Our submissions staff has been attempting to incorporate the report titles into the ToC as you requested,*

but has not been able to do so. The additional information apparently makes the file larger than the software is able to save and still keep links intact.

We would be happy, though, to provide you with a separate table cross-referencing report numbers and titles, but this information would not be hyperlinked to the rest of the dossier. Would that be helpful? Please let us know and we'll be happy to provide the cross-reference if you'd find it useful.

2) **Missing study:** There appears to be a missing study under 4.2.3.3.1 (In Vitro Genotoxicity). The Study identified as M-11-19-1 "In vitro mammalian Cell Gene Mutation Test" is a final report **amendment** consisting of 3 pages and refers to the [] study #G97CB86.702 original study which does not appear to be included in the NDA. The following study (M-11-186) is an analysis of the metabolites of TAK-375 expected from the — study. Please supply the original In vitro cell gene mutation test — study.

[Danielson, Steven (TGRD)] *The original study report is on its way to you today [Tuesday, 11/16] .*

3) **Loosely targeted links:** There are a number of loosely targeted links in the **Nonclinical Written and Tabulated Summary** sections. Following the link frequently directs the document in-between pages with the previous page containing the item of interest or if it is a link to a table you are sent to the first table of many in a series. Please see the following examples:

- In the **Pharmacology Written Summary** section, from the table of contents, Click on the link for **3.0 Secondary Pharmacodynamics** which should take you to the top of page 14. Instead you will find that it sends you in between pages 14 and 15 and you must scroll up to find the beginning of the section.
- If in subsection **3.1.1 Table 2.6.3.3 Report No. TAK-375/M-11-00323.001R** you click on the link to **Table 2.6.3.3** in the heading you will find it sends you to Table 2.6.3.1 while the table of interest, 2.6.3.3, is on page 8/14 in this set of tables. Clicking on this link should take you directly to the table without the need for searching within this set of tables.
- If in subsection **3.1.1** (the same subsection previously described) you were to click on the in-text **Table 3a** link, you should be directed to the table which is found at the top of p. 15 but instead you are sent to a place between pages 15 and 16.

This is an example of the type of loose links which occur throughout the Nonclinical Written and Tabulated Summary sections. You will also find that the reference links are loose in a similar manner. For example:

- Subsection **4.1.1 Table 2.6.3.4 Report Number TAK-375/M-11-00106.001A** (the link for table 2.6.3.4 has the same issues as previously described above). Reference **[17]** is cited multiple times in this section and directs you to many different places in the references which are usually below the reference or in-between pages. Only the occasional reference link takes you to a window in which you see the reference without scrolling up or down. This

is a frequent result of following reference links throughout the summary document.

[Danielson, Steven (TGRD)]I believe the situation you are describing occurs as the result of specific Adobe settings on the viewer's computer. All of the hyperlinks are established in accordance with the referenced Guidance. The Guidance further stipulates that all hyperlinks be set to 'inherit zoom', and we think that's the issue here. For example, if the 'fit window' setting is chosen, the entire page is visible on the screen; if the 'fit width' setting is selected, the hyperlink goes to the correct page, but you will only be able to see a portion of the page. If this explanation doesn't make sense, we can schedule a phone call at your convenience to discuss further

**Appears This Way
On Original**

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Sara Stradley
11/17/04 11:38:05 AM
CSO

Stradley, Sara

From: Stradley, Sara
Sent: Friday, November 12, 2004 10:07 AM
To: 'sdanielson@tgrd.com'
Cc: Stradley, Sara
Subject: Ramelteon NDA 21-782

Steve

We need the following issues addressed. We have had some trouble navigating the electronic submission and it appears the links need to be tightened. The missing study needs to be submitted prior to the filing date of Nov 21, 2004.

Sara

1) Table of contents request: In the Pharmtoc.pdf (Pharmtox Table of Contents) it would be significantly more useful if the Description column contained the study titles or at least an abbreviated description of the content of the study instead of being identified by study number. The column titled "Review copy volume location number" is unused and not necessary and could contain the study number/designation. Using the methodology of the following example for your table of contents would greatly aid review:

Description/Study Title	Study #	Archive copy location folder/file name
4.2.1 Pharmacology		
4.2.1.1 Primary Pharmacodynamics		
Effects of TAK -375 on melatonin receptors	M-11-00617	pharmtox\pharm\m-11-00617.pdf
Effects of TAK -375 and metabolite M-II on human MT ₂ receptor	M-11-00616.001	pharmtox\pharm\m-11-00616001r.pdf

2) Missing study: There appears to be a missing study under 4.2.3.3.1 (In Vitro Genotoxicity). The Study identified as M-11-19-1 "In vitro mammalian Cell Gene Mutation Test" is a final report **amendment** consisting of 3 pages and refers to the [] study #G97CB86.702 original study which does not appear to be included in the NDA. The following study (M-11-186) is an analysis of the metabolites of TAK-375 expected from the — study. Please supply the original In vitro cell gene mutation test — \ study.

3) Loosely targeted links: There are a number of loosely targeted links in the **Nonclinical Written and Tabulated Summary** sections. Following the link frequently directs the document in-between pages with the previous page containing the item of interest or if it is a link to a table you are sent to the first table of many in a series. Please see the following examples:

- In the **Pharmacology Written Summary** section, from the table of contents, Click on the link for **3.0 Secondary Pharmacodynamics** which should take you to the top of page 14. Instead you will find that it sends you in between pages 14 and 15 and you must

scroll up to find the beginning of the section.

- If in subsection **3.1.1 Table 2.6.3.3 Report No. TAK-375/M-11-00323.001R** you click on the link to **Table 2.6.3.3** in the heading you will find it sends you to Table 2.6.3.1 while the table of interest, 2.6.3.3, is on page 8/14 in this set of tables. Clicking on this link should take you directly to the table without the need for searching within this set of tables.
- If in subsection **3.1.1** (the same subsection previously described) you were to click on the in-text **Table 3a** link, you should be directed to the table which is found at the top of p. 15 but instead you are sent to a place between pages 15 and 16.

This is an example of the type of loose links which occur throughout the Nonclinical Written and Tabulated Summary sections. You will also find that the reference links are loose in a similar manner. For example:

- Subsection 4.1.1 Table 2.6.3.4 Report Number TAK-375/M-11-00106.001A (the link for table 2.6.3.4 has the same issues as previously described above). Reference [17] is cited multiple times in this section and directs you to many different places in the references which are usually below the reference or in-between pages. Only the occasional reference link takes you to a window in which you see the reference without scrolling up or down. This is a frequent result of following reference links throughout the summary document.

*Appears This Way
On Original*

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Sara Stradley
11/12/04 01:27:22 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

10/21/04
Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-782

Takeda Global Research & Development Center, Inc.
475 Half Day Road
Lincolnshire, Illinois 60069

Attention: Steve Danielson
Manager, Regulatory Affairs

Dear Mr. Danielson:

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: L J (ramelteon) Tablets
Review Priority Classification: Standard (S)
Date of Application: September 21, 2004
Date of Receipt: September 22, 2004
Our Reference Number: NDA 21-782

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 21, 2004 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be July 22, 2005.

Under 21 CFR 314.102(c), you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

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. We note that you have not fulfilled the requirement. We acknowledge receipt of your request for a deferral of pediatric studies for this application. Once the application has been filed, we will notify you whether we have deferred the pediatric study requirement for this application.

NDA 21-782

Page 2

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthetic, Critical Care and Addiction Drug Products (HFD-170)
Attention: Division Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions call me at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Sara E. Stradley, MS
Regulatory Project Manager
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Sara Stradley
10/21/04 08:01:29 AM

**PRESCRIPTION DRUG
USER FEE COVER
SHEET**

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website. <http://www.fda.gov/cder/pdofa/default.htm>

<p>1 APPLICANT'S NAME AND ADDRESS Takeda Global Research & Development Center, Inc. 475 Half Day Road Lincolnshire, IL 60069</p>	<p>4 BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER 21-782</p>
<p>2 TELEPHONE NUMBER (Include Area Code) (847) 383-3179</p>	<p>5 DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA)</p>
<p>3 PRODUCT NAME L J. ramelteon</p>	<p>6 USER FEE ID NUMBER 4763</p>

7 IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box)	<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)

8 HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

YES NO
(See item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration CDER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	and Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number
--	---	---

<p>SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE </p>	<p>TITLE Manager, Regulatory Affairs</p>	<p>DATE 9/15/2004</p>
---	--	---------------------------



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

3/9/04

IND 58.136

Takeda Global Research & Development Center, Inc.
475 Half Day Road
Lincolnshire, IL 60069

Attention: Tracy Lynch
Program Manager, Regulatory Affairs

Dear Ms. Lynch

Please refer to the teleconference meeting between representatives of your firm and FDA on February 11, 2004. The purpose of the meeting was to discuss the clinical development program of ramelteon (TAK-375).

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Sara E. Stradley
Regulatory Project Manager
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

SPONSOR MEETING ATTENDEES

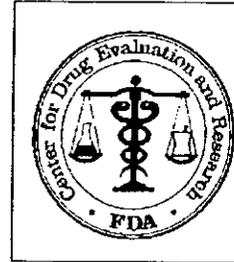
Meeting Date: February 11, 2004

Location: teleconference

Application: IND 58.136

Drug: Ramelteon (TAK-175)

Indication: Treatment of insomnia



Sponsor: Takeda Global Research & Development Center, Inc.

Type of Meeting: Guidance

Minutes Recorder: Sara Stradley, M.S., Regulatory Project Manager

Takeda	Title
Claire Thom, Pharm.D.	Vice President, Research and Development
Stephen Sainati, M.D., Ph.D.	Vice President, Clinical Research
Mick Roebel, Ph.D.,	Vice President, Regulatory Affairs
Leslie Koehler, B.S., MBA	Associate Director, Regulatory Affairs
Frank Ogrinc, Ph.D.	Manager, Statistics
Steve Danielson, B.S.	Manager, Regulatory Affairs
Sherry Weigand, M.D., Ph.D.	Program Manager, Clinical Research
[Consultant
Tracy Lynch, B.S.	Program Manager, Regulatory Affairs
Kirsten Dale, B.S.	Senior Associate, Regulatory Affairs
FDA/ HFD-170	Title
Bob A. Rappaport, MD	Division Director
D. Elizabeth McNeil, MD	Medical Reviewer
Rigoberto Roca, MD	Deputy Director
Tom Permutt, PhD	Statistical Team Leader
Dionne Price, PhD	Statistical Reviewer
Adam Wasserman, PhD	Pharm Tox Reviewer
Sara Stradley, MS	Regulatory Project Manager

Meeting Objective: The purpose of the meeting was to provide comments on the clinical development program.

General Discussion: After brief introductions, the meeting focused on general comments and the questions from the January 30, 2004, meeting package.

General Comments

The Division stated that a drug for chronic insomnia should demonstrate efficacy in a real world setting, i.e., outpatient. The Division noted the Sponsor's hypothesis that the novel mechanism of action of their product makes it difficult for people to appreciate the shortened latency to persistent sleep (LPS) and increased total sleep time (TST) provided by ramelteon. The Division also noted the Sponsor's hypothesis that the efficacy of ramelteon may be more vulnerable to the effects of poor sleep hygiene than benzodiazepine receptor agonists (BZRA) and more vulnerable to the effects of variation in the timing of test drug administration relative to bedtime. The Division stated that the Sponsor should design an outpatient study that demonstrates efficacy while taking into account unique properties of the product. The Sponsor stated that study 025 (elderly, outpatient study), is identical in design to study 020 (18-64 year olds) and inquired if study 025 would be acceptable if it met its primary objective. The Division stated that it would need to review the study design and study report before commenting on study 025. The Division stated that it might be possible to extrapolate efficacy to the younger population based on the results of study 025, but this would depend on the results of the study. The Sponsor stated that study 025 is complete and the database will be locked at the end of the month.

The Sponsor inquired about Clinical Global Impression (CGI). The Division stated that they would be willing to consider this as a secondary endpoint

The Sponsor questioned whether study 025 would support an NDA filing and approval. The Division stated that the final study report would need to be reviewed before commenting on study 025. The Sponsor stated they would add another study with a nontraditional outcome variable (i.e., CGI) and would request comments from the Division on the study design. The Division reminded the Sponsor to note this request clearly in the cover letter.

The Division asked for clarification of the studies mentioned in the meeting package and whether any additional studies were planned. The Sponsor stated

Questions

Question 1. Are subjective data obtained only in the inpatient (ie, sleep laboratory) environment, using the post-sleep questionnaire, sufficient to document positive patient-reported efficacy, together with the PSG data?

The Division stated that subjective data obtained only in an inpatient environment using the post-sleep questionnaire together with objective polysomnography (PSG) data will not suffice to document positive-patient reported efficacy.

Question 2. If the answer to question 1 is yes, need these inpatient subjective assessments of efficacy be a prespecified endpoint? If these endpoints must be specified a priori, need they be identified as primary endpoints?

The Division stated that this question is not applicable based on the response to question 1.

Question 3. If both inpatient and outpatient subjectively reported efficacy is required, would the following combination of data be acceptable evidence of efficacy:

- a. Clinically meaningful and statistically significant improvement in LPS and TST versus placebo using PSG.*
- b. Statistically significant improvement versus placebo using responses to post-sleep questionnaires in the sleep laboratory.*
- c. Supportive findings in patient reports of efficacy at home, which may or may not achieve formal statistical significance.*

The Division stated that the proposed combination would not be acceptable.

Action Item

The Sponsor stated that study 025 (elderly, outpatient study), is identical in design to study 020 (18-64 year olds) and inquired if study 025 would be acceptable if it met its primary objective. The Division stated that it would need to review the study design and study report before commenting on study 025. The Sponsor should submit the study to HFD-170.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Sara Stradley
3/9/04 10:17:03 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 58,136

1/12/04

Takeda Pharmaceuticals North America, Inc.
475 Half Day Road
Lincolnshire, IL 60069

Attention: Tracy Lynch
Program Manager, Regulatory Affairs

Dear Ms. Lynch:

Please refer to the meeting between representatives of your firm and FDA on December 15, 2003. The purpose of the pre NDA meeting was to discuss the content and format of the chemistry, manufacturing and controls section of the NDA for ramelteon (TAK-375).

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Sara E. Stradley, MS
Regulatory Project Manager
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

Industry Meeting Minutes

Date/Time: December 15, 2003 / noon

Location: Parklawn, Potomac Conference Room

Application: IND 58,136

Sponsor: Takeda Pharmaceuticals North America, Inc.

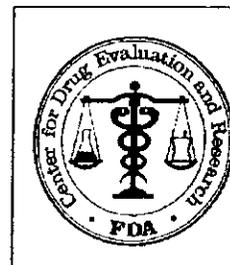
Drug: Ramelteon (TAK-375)

Indication: insomnia

Type of Meeting: pre NDA (CMC only)

Meeting Chair: Bob Rappaport, Division Director

Minutes Recorder: Sara Stradley, M.S., Regulatory Project Manager



Takeda	Discipline
Steven Glenn	Manager, CMC
James Morley, PhD	Director, Pharmaceutical Development and Supplies
{	CMC Consultant
Steven Danielson	Manager, Regulatory Affairs
Tracy Lynch	Program Manager, Regulatory Affairs
Aziz Karim, PhD	Vice President, Clinical Phase I
Stephen Sainati, MD, PhD	Vice President, Clinical Research
David Baron, PhD	Director, Nonclinical Safety and Efficacy
FDA	Title
Bob A. Rappaport, MD	Division Director
Eric Duffy, PhD	Director, Division of New Drug Chemistry II
Dan Mellon, PhD	Supervisor, Pharmacology/Toxicology
Ravi Harapanhalli, PhD	Acting, Chemistry Team Leader
Dominic Chiapperino, PhD	Chemistry Reviewer
Adam Wasserman, PhD	Pharmacology/Toxicology Reviewer
David Lee, PhD	Clinical Pharmacology Reviewer
Sara Stradley, MS	Regulatory Project Manager

Meeting Objective(s): The purpose of pre NDA meeting was to discuss the content and format of the chemistry, manufacturing and controls (CMC) section of the NDA for ramelteon (TAK-375).

General Discussion: Following introductions, the discussion focused on the Sponsor's questions that were included in the October 28, 2003 meeting package. The Sponsor's questions are presented below in italicized text. Agency responses, prepared prior to the meeting and presented on slides, are in italics. Discussion is presented in normal text.

Pre Clinical Comments

Based on the review of the CMC package:

- [] are specified at levels above the [] threshold for qualification. Regarding these impurities:
 - Adequate qualification based on toxicology studies has been demonstrated
 - Appropriate genetic toxicology qualification has not been conducted
 - each isolated impurity will require testing up to its limit dose in two in vitro genetic toxicology assays []

Discussion

The Division stated that although genetic toxicology studies have been conducted with TAK-375 batches containing the impurities [] each impurity exceeding the ICH threshold for qualification must be tested in isolation in two *in vitro* genetic toxicology studies as described.

Drug Substance

Question A: Please comment on the suitability of the test items and proposed limits included in the drug substance specifications

FDA RESPONSE

- [] should be retained in the specifications.
- Developmental data regarding [] should be provided.
- Clarification regarding related impurities:
 - [] impurities specified with limits of NMT [] would need to be qualified.
 - The limit of [] is the qualification threshold.
- Proposed [] specification of [] should be justified based on the manufacturing process and the drug product formulations.

Discussion

The Division stated that the [] should be retained in the specifications for further assurance of identification and purity. The Division stated that information [] should be provided so that appropriate specifications can be established for the [] in the drug substance. The Sponsor agreed to do so.

The Division requested that the Sponsor justify the proposed particle specification. The Sponsor agreed to do so.

Question 1: Does the Division agree with the stability plan for the drug substance outlined in Section 1.5, table 1 f, especially concerning site-specific lots?

FDA RESPONSE

- Stability data from the pilot scale lots manufactured at the Osaka site can be submitted with the NDA as supporting data.
- The data used to determine the retesting period should be generated at the proposed commercial site.
- Stability updates may be filed following the submission of the NDA.

Additional Comments:

- The starting material is identified as [redacted]. Therefore, a detailed description of the synthetic process starting from [redacted] should be included in the NDA.
- [redacted] testing should specifically include testing for [redacted]. The methods validation should establish that the [redacted] measured would include these [redacted] if present. If not, a separate test for [redacted] may need to be proposed.

Discussion

The Division stated that the stability data from the Osaka site could be submitted as supporting data. The stability data should be generated at the proposed commercial site. The Division advised the Sponsor to provide all of the details from both sites and highlight any differences. The Sponsor stated that they might have at least [redacted] of stability data from the commercial site at the time of NDA filing. The Sponsor stated that they would like to get a [redacted] expiry period based on the [redacted] stability data from the pilot study. However, the Division stated that the stability data should be generated at the commercial site and that, even if a limited expiration dating is granted at the time of NDA approval, the firm could extend the expiration dating based on the real time data from the three primary stability batches and that such extensions may be documented in the annual report. The Division also clarified that the sponsor should present clear scientific justification, including environmental and manufacturing similarities and other relevant factors between the pilot scale production site versus that of commercial scale production, for the Division to consider the stability data on the pilot scale batches in granting expiration dating at the commercial site. The Sponsor asked if additional stability data could be submitted during the review cycle. The Division stated that it is best to submit data early in the review cycle to allow sufficient time for review.

The Division stated that it was unclear about the starting material and that the Sponsor should provide a detailed description of the synthetic process starting from [redacted] in the NDA. The Sponsor stated that they plan to submit this information. The Sponsor stated that this information was provided to HFD-120 and the Division requested that the full description be sent to the HFD-170.

The Sponsor stated that their [] does include []
[] However, the [] testing protocol currently does not specifically
[] They noted that they are committed to addressing this concern.

Drug Product

Question 2: Does the Agency agree with the plan for request for waiver of demonstration of in vivo bioequivalence and the data form that is proposed? A preliminary evaluation by the Office of Clinical Pharmacology and Bioequivalence of the results provided with this submission is requested with respect to adequacy of support for waiver.

FDA RESPONSE

- *BE waiver request may be reasonable, if additional information on permeability assessment (i.e., in vitro test) is available, to support the existing metabolism data.*

Discussion

The Division stated that the solubility data appears to be acceptable. However, additional data on the permeability assessment is needed to support the mass balance information. The Sponsor stated that they do have supporting data. A food effects study has been done and the AUC remains the same, although Cmax is decreased with food consumption. The Division stated that they would have to review this data before commenting on it. The Sponsor will provide this information for the Division's review. Additionally, the Sponsor will search for any in-house *in vitro* information on permeability assessment and submit it to the Agency as well.

Question 3: Please comment on the overall suitability of the proposed drug product specifications.

FDA RESPONSE

- *Issues with impurities and dissolution testing are addressed separately.*
- *Provide additional specification for [] testing*
- *Provide additional specification for []*
- *The following [] should be established:*
 - *[] testing, sampled from specified locations []*
 - *[] testing, from []*
- *Tests measuring tablet size, weight, friability, and hardness*

Discussion

The Division stated that the Sponsor should provide specifications for []
[]. Additional [] should be established that
include [] measurement of tablet size,
weight, friability and hardness. The Sponsor stated that they are collecting this data.

Question 4: TPNA's plan for setting the NDA related substance limits for the drug product is based on application of ICH identification and qualification thresholds. Does the Agency concur with the proposals?

FDA RESPONSE

- *Degradants detected at the threshold level of [] would need to be identified.*

- *The Agency agrees with your proposed limit of NMT [] for any individual impurity not qualified.*

Discussion

The Division stated that degradants detected at threshold would need to be identified. The Sponsor stated that [] and they will propose a specification of [] The Division stated that while this appears acceptable, the final toxicological determination will be made on review based on the chemical nature of the degradant and the extent to which it is formed []

Question 5: Are the conditions selected for dissolution test methodology and the proposed specification acceptable for regulatory purposes?

FDA RESPONSE

- *The drug is being proposed as a BCS Class I since it is highly soluble, highly permeable, and the dosage form is rapidly dissolving. Therefore, Q of ~ at 15 minutes should be established.*
- *The justification for the chosen conditions should include a discussion on the discriminatory power of the method with regard to the formulation and the process.*

Discussion

The Division stated that the specification proposed by the Sponsor is too broad. The Division stated that specifications should not be set so that it will consistently []. If it does not [] testing would be done based on USP<701>, which provides for additional allowance for wider ranges. The specifications should be tight enough to discriminate between bio-equivalent and non-equivalent batches and should reflect BCS Class I classification, if in fact all data indicate that this is the appropriate class.

The firm indicated that, based on their data, they may be able to propose the Agency-recommended specification of Q = ~ in 15 minutes, however, Q = ~ in 15 minutes would be a realistic proposal. The Division stated that the firm should submit the detailed dissolution data including multiple time points and that a determination of Q = [] at 15 minutes would be made during the NDA review.

Question 6: Does the Division agree with stability plan for drug product outlined in Section 2.6, Table 2v, especially with respect to expectations for site-specific stability data from the commercial manufacturing location?

FDA RESPONSE

- *The Agency is satisfied with your stability plan. However:*
 - *The data from the Osaka facility will be considered supporting in nature.*
 - *The limited amount of data from the commercial site will impact the initial expiry period that might be granted.*
 - *A detailed description of the post-approval stability program should be submitted in the NDA.*
 - *Updates to the stability data can be submitted within the review cycle*

Discussion

The Division stated that the data from the Osaka facility would be considered supportive data, since there appear to be significant environmental and other differences between the Osaka facility located in Japan and the intended commercial site located in Ireland. The Sponsor should provide at least 12 months of stability data from the commercial site. As stated previously, although a limited expiration dating is granted at the time of NDA approval, the firm may extend the expiration dating based on the real time stability data on the three primary batches and may often report such an extension in the annual report, unless certain issues are identified during the NDA review that may require a prior-approval supplement for this extension. The Division noted that the site differences for the drug product are much more significant than those for the drug substance, since the proposed commercial site for the drug product is in Europe whereas the pilot scale batches were manufactured in Japan. However, for the drug substance, both the pilot scale site and the commercial site are in Japan and are within the same proximity. Therefore, the stability data from the pilot scale batches would be deemed supportive in nature and ICH Q1E guidelines would be followed in extending the expiration dating beyond the real time data, if such an extension is permissible.

Question 7: Based on the approach in ICH guidance Q1E that allows assignment of expiration dating that exceeds the period of available long-term data by up to 12 months, will a proposal to assign a 12 month shelf-life for this product with a good demonstrated stability profile through 12 months of long term storage (3 lots, pilot scale commercial packaging) be acceptable?

FDA RESPONSE

- The 12 months of stability data on the pilot scale batches would be considered supporting data.
- The stability data from the commercial site would be considered primary data.
- Issues regarding appropriate extrapolation and site-specific stability data would be important in determining the expiry period (See comments for next question regarding extrapolation).

Discussion

As stated previously by the Division, the 12 months of stability data on the pilot scale batches would be considered supportive data. The data from the commercial site would be the primary data used for the expiry dating.

Question 8: If not, can the Agency provide TPNA an overview of the current policy for assignment of expiration dating periods to drug products, with respect to extrapolation beyond the range of real-time storage results, to aid our understanding of reasonable expectations for this and future products? To what extent is reliance on statistical analysis and proposals found in Q1E generally acceptable?

FDA RESPONSE

- For a summary of the Agency's current policies and preferences in these matters relating to expiration dating, the decision tree in Appendix A (p.7) of Q1E can be referenced.
- Summary of Agency considerations for 12 month extrapolation
 - no significant changes under accelerated conditions
 - no significant changes in long-term data
 - data is amenable to statistical analysis
 - the results of statistical analysis support additional 12 months of shelf-life
 - knowledge of the degradation pathways

Discussion

The Division stated that the decision tree in Appendix A of Q1E should be referenced for the current policies on expiration dating.

Question 9: Is the proposal outlined in Section 3.1 for submission of executed batch records acceptable?.

FDA RESPONSE

- *Yes. Submission of batch records for 1 lot of each tablet strength (4, 8, and 16 mg) from both pilot batches and clinical study batches is acceptable.*
- *The Agency also would like submission of batch records for 1 lot of each tablet strength from batches made at TIL.*

Discussion

The Division stated that the proposal is acceptable.

CTD Format

Question 10: Are there any specific requirements or requests related to CTD formatting, beyond those contained in the official guidance documents, which should be considered in preparation of the electronic submission, to aid in the review of Module 3?

FDA RESPONSE

- *Stability data should be submitted in SAS Transport files and should be extractable for ease of statistical analysis.*
- *Refer to the following link for details on the format and content of eCTD
<http://www.fda.gov/cder/regulatory/ersr/ectd.htm>*
- *Refer to the link to the docket for information (memorandum 27) on the process for submitting an eCTD. <http://www.fda.gov/ohrms/dockets/dockets/92s0251/92s0251.htm#Center%20for%20>*
- *Direct questions about your electronic submission to the following email address esub@cder.fda.gov (follow the procedure in memorandum 27).*

Discussion

The Division stated that the stability data should be submitted in SAS transport files. The Division also provided electronic links to information on electronic submissions and CTDs.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Sara Stradley
1/12/04 04:55:15 PM

MINUTES OF TELECONFERENCE MEETING
CMC End of Phase II
IND 58,136

DRUG: TAK-375
SPONSOR: Takeda America Research & Development Center, Inc.
INDICATION: []
DATE/TIME: January 17, 2003/1:30PM
LOCATION: Conference Room E; WOC2

ATTENDEES: Division of Neuropharmacological Drug Products:

Tom Oliver, Ph.D. CMC Team Leader
Don Klein, Ph.D. CMC Reviewer
Melaine Shin, R.Ph.

Takeda Pharmaceuticals North America, Inc:

Ms. Tracy Lynch, Sr. Associate, Regulatory Affairs
Mr. Steven Danielson, Manager, Regulatory Affairs
Dr. James Morley Ph.D., Director, Pharmaceutical Development &
Supplies
Mr. Steven Glenn, Manager, CMC
[]
[] , Consultant, CMC

DISCUSSION:

- *Does the Agency agree with Takeda's proposal that [] be designated as [] for purposes of GMP compliance, in accordance with the criteria of ICH guidance Q7A? If so, will it be necessary to provide process and control information concerning the manufacture of [] in the planned NDA filing?*

FDA agreed that [] could be designated as a [] []. However, since the FDA/ICH guidance [] is currently under discussion, TPNA should check back with the Agency on this issue in the future. [] acceptance specifications should be included in the NDA, and that at least one batch of TAK-375 manufactured using [] from each vendor source should be included in the stability program.

- *Are there comments on any other specific items in the development plan outlined in the briefing package, concerning issues that should be addressed either in phase III or in preparation for an NDA?*

FDA indicated that the sponsor should ensure that any DMF that is referenced in the NDA is up to date, and include a statement in the DMF or NDA that the commercial packaging has been previously CDER approved. For discussion on CDER approved packaging, refer to Attachment C in the "Changes to an Approved NDA or ANDA" Guidance, November 1999.

- FDA advised the sponsor to have an official name assignment from USAN.
- TPNA should ensure their [] specifications are consistent with the ICH Q3B Guidance "Impurities in New Drug Products", 1996. It was agreed that TPNA will be submitting 12 month real time and 6 month accelerated stability with the NDA, as the FDA was concerned that if less stability data was submitted, new impurities might appear during NDA review, resulting in additional review issues in the allotted 10-month PDUFA time frame.
- FDA requested that TPNA include [] also requested that physician samples and managed care packaging be part of the NDA stability program. FDA also suggested that TPNA follow the draft stability guidance "Stability Testing of Drug Substances and Drug Product", June 1998, pointing out the information required under Section K. "Degradation Products".
- FDA inquired about the proposed drug product formulation change and TPNA responded that the formulation change would consist of a change [] FDA suggested that any formulation change should be discussed with the Biopharmaceutics Division to ensure that a BE study is not required. TPNA stated that they plan to submit the formulation change in a CMC amendment to the IND and include a request for review by the Biopharmaceutics Division in the cover letter.
- FDA indicated that the [] specification as presented on page 27, Table 2. G "current specifications for TAK-375 4mg, 8mg, 16mg, and 32mg" of the Briefing Document is not adequate; TPNA should report individual impurities at Phase III and on stability, in addition to the current requirement []
- FDA stated that the specification set for drug substance must be reviewed and agreed upon by the Pharmacology/Toxicology review team. TPNA agreed to provide justification for qualification of the impurities in NDA.
- FDA encouraged TPNA to determine the [] If unsuccessful, TPNA should provide justification, describe its efforts to determine the structures, and discuss the possible chemical reasons for these impurities.

/S/

Melaine Shin, R.Ph.
Meeting Recorder

/S/

Thomas Oliver, Ph.D.
Meeting Chair

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Thomas Oliver
5/7/03 08:32:58 AM

MEMORANDUM OF MEETING MINUTES

Meeting Date: November 8, 2001 Time: 1:00 pm Location: WOC II Rm 4023

Application: IND 58,136; TAK-375
Indication: []
Type of Meeting: Discussion of Development Plan
Meeting Chair: Russell Katz, M.D.
Meeting Recorder: Melaine Shin, R.Ph.

FDA Attendees:

Russell Katz, M.D., Division Director Tom Laughren, M.D., Team Leader
Robert Levin, M.D., Clinical Reviewer Ramana Uppoor, Ph.D., Biopharm TL
Wendy Chou, Pharm.D. Ph.D., Biopharm Barry Rosloff, Ph.D., Pharmacology TL
Controlled Substance Staff: Katherine Bonson, Ph.D., Corinne Moody, R.Ph.

Takeda & Consultant Attendees:

Charlene Stubbs, Ph.D. David Baron, Ph.D.
Ingrid Hoos Steve Danielson
[] Roger Meyer, M.D.
Gary Richardson, M.D. James Longstreth, Ph.D.

Below are the proposed discussion points and appropriate FDA feedback:

1. []

Response: []

J

J

2. [

Response:]

3. TPNA plans to conduct studies in transient and chronic insomnia utilizing patients in sleep labs and in outpatient studies. In addition, a six month, double-blind, placebo-controlled efficacy trial is planned. Provided a positive outcome, would the Agency consider this trial sufficient to support long term administration of TAK-375?

Response: We indicated that a 6 month trial would support a statement regarding efficacy up to 6 months, but it would also be important to have safety data to cover such use, including careful assessment of withdrawal emergent symptoms after treatment for such a duration.

4. The development plans currently include studies designed specifically to address demonstration of the lack of abuse potential and dependency. The plan includes both animal and human models that have been demonstrated to be differentiating. Based on the pre-clinical profile of TAK-375, are all of these proposed studies necessary to obtain a non-scheduled classification for TAK-375? If the Agency determines that these studies are important, does the Agency agree that this is an acceptable strategy to obtain a non-scheduled classification (provided a satisfactory outcome is obtained)?

Response from CSS:

- TAK-375 is a new molecular entity that has not been fully characterized pharmacologically. Specifically, this drug has not been characterized in terms of its abuse potential.
- The proposed studies are necessary for a full characterization of TAK-375 and appear to be well designed to evaluate the abuse potential of TAK-375. However, full protocols for the studies should be submitted.
- The dose for the monkey studies should include low, medium and high doses. The high doses should produce plasma levels that are 2-3 times the plasma levels of the highest proposed therapeutic dose of TAK-375.
- The dose-finding clinical study does not describe how dose-escalation beyond 64 mg/70 kg will occur. Ideally, high doses that are 2-3 times the proposed therapeutic doses will

be administered, but it is unclear how any adverse events will be managed.

- Based on the results of monkey studies, additional clinical studies may be required in the future.
 - TAK-375 will be evaluated for abuse potential solely in comparison to control conditions.
5. The primary insomnia (transient and chronic) [] development programs would require that approximately 2000 patients, 500 of whom will be elderly, be exposed to TAK-375 treatment during its development. In addition, a long-term open label study is intended to provide safety data for approximately 300 patients for a duration of six months and approximately 100 patients for a duration of one year. Does the Agency concur that this approach provides the required safety data for the submission of both indications?

Response: We indicated that the plan for safety was generally acceptable.

6. The development programs for the primary insomnia [] indications are overlapping with respect to the many requirements for drug development and approval. A single regulatory submission is planned for both indications, provided positive outcomes to the Phase III primary insomnia (transient and chronic) [] development studies are achieved. Is this an acceptable submission strategy?

Response: We had no objection to the plan to submit the primary insomnia [] claims at the same time.

Additional Comments from OCPB:

- From the Clinical Pharmacology and Biopharmaceutics perspective, there are numerous factors that could contribute to the variability in the PK of TAK-375 and could potentially contribute to safety and efficacy concerns of TAK-375 in the target patient populations. Therefore, it is important in the overall drug development plan to integrate all the attributable factors to the variability of PK, explore exposure-response (PK/PD) relationship and define optimal dosing strategy for the subgroups and individuals in the target patient population. Population approach in trials where proper response endpoints are measured to exploring PK and PK/PD should be considered where appropriate. In addition, the plan should also incorporate the following: M-II, the active metabolite and major circulating moiety, and potential additive effect to the PK of TAK-375 from multiple attributable factors to the PK variability. We note that the following three dose ranging studies to explore dose-response relationship or safety/efficacy of TAK-375 are planned: (1) Dose-response evaluation in patients with chronic insomnia; (2) Dose ranging in the elderly patients with chronic insomnia to evaluate safety and efficacy; (3) []
 [] From the meeting, you indicated that you are exploring the inhibitory effect of major circulating metabolite M-II on the P450s isozymes as well as the binding affinity of M-II to various receptors. You also indicated that the PK information gathered from the traditional PK studies will be integrated into the drug development plan using population approach as appropriate and you will discuss further with the Agency regarding this matter in the future.
- We note that the relative importance of individual isozymes (CYP2C9, 3A4, and 1A2) to the overall metabolic fate of TAK-375 is currently undetermined. We recommend that you incorporate the following into your drug development plan: (1) the relative importance of isozymes including CYP2C9, 3A4 and 1A2 to the overall metabolic fate of TAK-375, (2) explore the potential impact

of CYP2C9 enzyme polymorphism on the PK and response of TAK-375, (3) explore the ethnic difference of CYP2C9 activity in the metabolism of TAK-375, and (4) incorporate relevant information into studies exploring PK and PK/PD relationship of TAK-375.

Minutes Preparer: _____
Melina Fanari, R.Ph.

Chair Concurrence: _____
(or designated signatory) Thomas Laughren, M.D.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Russell Katz
5/10/02 10:54:10 AM