

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-782

CHEMISTRY REVIEW(S)

NDA 21-782

Rozerem (Ramelteon) Tablets, 8 mg

CHEMISTRY DIVISION DIRECTOR REVIEW

Applicant:

Takeda Global Research and Development Center
475 Half Day Road
Lincolnshire, IL 60069

Indication: Once daily treatment for insomnia

Presentation: Supplied in bottles as 30s, 100s, and 500s, and in blisters as 3s.

EER Status: Acceptable 11 July 2005

Consults: Trade name review acceptable as Rozerem, 21-JUN-2005
Statistics - 3 months expiration date recommendation
Medical - dissolution specification of Q at 15 min time point
EA - no consult - waiver requested - granted

Post Approval Agreements: None

The original NDA was dated 21-SEP-2004, and chemistry review #1 with CMC deficiencies was entered into DFS on 10 June 2005. Amendment 18, dated 22-JUN-2005, was submitted in response to the Agency communication dated 10-JUN-2005. Chemistry review #2 was completed on 29-JUN-2005, with the overall cGMP compliance as acceptable to the Office of Compliance on 11-JUL-2005.

The Ramelteon **drug substance** is manufactured from the [redacted] at Takeda-Japan (CFN#9610307). The batch size is [redacted]

[redacted] is manufactured from [redacted] (CFN# [redacted]). The batch size is [redacted] starting material is made from [redacted] under contract at [redacted]. The batch size is [redacted]. There is no comparability protocol for [redacted] at the time of change of supplier from [redacted]. Fate of potential impurities in [redacted] was justified with impurity [redacted] experiments in APIs [redacted]. There is significant analytical information on [redacted] batches of API to justify process capability to produce [redacted] pure API.

Ramelteon is an indenofuran NME with high affinity and selectivity for human melatonin receptors (MT1 and MT2). Ramelteon has one chiral center, and the (S) form was developed since this form is about [redacted] times more potent at the MT1 receptor than the [redacted]

— form. ADME studies with C-14 radiotaged Ramelteon has shown very little parent drug. Ramelteon is highly soluble in aqueous solutions and readily partitions into octanol, thus justifying its cell permeability and long duration of action (once daily). Ramelton is not hygroscopic, is unable to support microbial burden, has no known polymorphs, and is stable under normal storage conditions when protected from light. Ramelteon undergoes

Conclusion

Drug substance is satisfactory.

The Ramelteon **drug product** is a film coated tablet of 8 mg manufactured at Takeda-Ireland (CFN# 9616691). The batch size is [] tablets.

Ramelton tablet 8mg is a conventional dosage form with no novel excipients. Core tablet weight is 130 mg, and the film coated tablet weight is 135mg. Compendial grade inactive ingredients are used. [] and not in USP. Iron oxide in printing ink complies with 21 CFR 73.1200. Takeda has certified that lactose monohydrate diluent is sourced from [] collected under conditions used for human consumption and that magnesium stearate is of []

Immediate release oral tablet design was chosen based on high solubility and oral absorption for Ramelteon. The manufacturing method is a conventional []

[

The proposed carton and immediate container label bears the statement [

] Following discussions with the firm, an agreement was reached in a TCon on 22-JUL-2005 that this statement would be removed. Labeling is therefore acceptable, and container labels are qualified with manufactured for, manufactured by, and marketed by statements.

All associated DMFs are acceptable

The overall Compliance recommendation is pending as of 11-JUL-2005.

Overall Conclusion

From a CMC perspective the application is recommended approvable.

Eric P. Duffy, PhD
Director, DNDC II/ONDC

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/s/

Eric Duffy
7/22/05 01:48:35 PM
CHEMIST



NDA 21-782
Ramelteon Tablets, 8mg.

Takeda Global Research & Development Center Inc. (TGRD)

Chemistry review # 3 by
Dr. Pramoda Maturu, PhD, MBA, HFD-820, for
Division of Anesthetic, Critical Care & Addiction Drug Products
(DACCAD)

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P DRUG PRODUCT [Name, Dosage form].....	Chem Rev #1
A APPENDICES	Chem Rev #1
R REGIONAL INFORMATION	Chem Rev #1
Review Of Common Technical Document-Quality (Ctd-Q) Module 1	
A. Labeling & Package Insert	Chem Rev #1
B. Environmental Assessment Or Claim Of Categorical Exclusion	Chem Rev #1
II. [] shelf life, revised container labels, and no pending agreements	11
III Agreement to be communicated - None	



Chemistry Review Data Sheet

1. NDA 21-782
2. REVIEW #: 3
3. REVIEW DATE: 21 July 2005
4. REVIEWER: Dr. Pramoda Maturu, PhD, MBA

5. PREVIOUS DOCUMENTS:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original submission #000	21 Sep 2004
Response to FDA Request	14 Jan 2005
Amendment 011	23 March 2005
Amendment 014	21 April 2005
Chemistry Review # 1	10 June 2005
CMC deficiencies communication	10 June 2005
Amendment 018	22 June 2005
Chemistry Review # 2	29 June 2005
Amendment 021	30 June 2005
Amendment 022	8 July 2005

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment	22 July 2005
Amendment 023 (BL-PPI)	18 July 2005
Amendment 022 (BL)	28 June 2005

7. NAME & ADDRESS OF APPLICANT:

Name: Takeda Global Research & Development Center
(TGRD)

Address: 475 Half Day Road, Lincolnshire, IL 60069

Representative: Mr. Steve Danielson

CHEMISTRY REVIEW

Chemistry Review Data Sheet

Telephone: 847-383-3179

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Rozerem™
b) Non-Proprietary Name (USAN) Ramelteon
c) Code Name/# (ONDC only) TAK-375, T99375, CAS# 196597-26-9
d) Chem. Type/Submission Priority (ONDC only):
• Chem. Type **1**
• Submission Priority **S**

9. LEGAL BASIS FOR SUBMISSION: FDC Act, 21 CFR 314.50, and 505(b)(1)

10. PHARMACOL. CATEGORY: Once daily treatment for insomnia.

11. DOSAGE FORM: Code 502 or 504; Pale orange yellow color film coated round and biconvex tablet with "TAK" and "RAM-8" printed on one side (Amendment # 23).

12. STRENGTH/POTENCY: 8 mg

13. ROUTE OF ADMINISTRATION: Code 001; orally taken within 30 min prior to bedtime with or without food.

14. Rx/OTC DISPENSED: Rx OTC

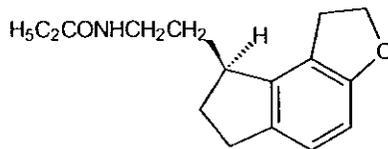
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Ramelteon, TAK-375, is an orally active sleep-promoting agent that is chemically designated as (*S*)-*N*-[2-(1,6,7,8-tetrahydro-2*H*-indeno-[5,4-*b*]furan-8-yl)ethyl]propionamide and contains one chiral center. The submission being reviewed is for the (*S*)-enantiomer, with an empirical formula of C₁₆H₂₁NO₂, molecular weight of 259.34, and the following chemical structure:



CHEMISTRY REVIEW

Chemistry Review Data Sheet

Each tablet includes the following inactive ingredients: lactose monohydrate, starch, hydroxypropyl cellulose, magnesium stearate, hypromellose, copovidone, titanium dioxide, yellow ferric oxide, polyethylene glycol 8000, and ink containing shellac and synthetic iron oxide black.

17. RELATED/SUPPORTING DOCUMENTS: IND 58,136 and J.Med.Chem. 2002, 45, 4222

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
\	II	\	\	1	Adequate	3 June 2005 Prmod Maturu	\
	III			1	Adequate	5 Aug 2004 Sarah Pope	Currently marketed
	III			1	Adequate	13 Jun 2002 Jila Boal	Currently marketed
	III			1	Adequate	6 Jan 2005 Rapti Madurawe	Currently marketed
	III			1	Adequate	12 Jan 2005 Rapti Madurawe	Currently marketed
	III			1	Adequate	12 Jan 2004 Monica Cooper	Currently marketed
	III			1	Adequate	3 Mar 2005 Alan Schroeder	Currently marketed



CHEMISTRY REVIEW



Chemistry Review Data Sheet

✓	III	✓
---	-----	---

1	Adequate	25 Sep 2002 Gil Jong Kang	Currently marketed
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¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	— months expiration date (30s and — packages for assay)	June 7, 2005	Dr. Buenconsejo, PhD
EES	Overall compliance is acceptable.	July 11, 2005	
Pharm/Tox	Approved with phase IV commitments	June 22, 2005	Dr. Wasserman, PhD
Biopharm	Acceptable with labeling revisions (food effect)	June 21, 2005	Dr. Lee, PhD
LNC	N/A		It is a simple IR form and the established name is the USAN name.
Methods Validation	Not requested; The Methods are conventional and do not qualify for any of the ONDC interim criteria for MV.		
ODS/DMETS	Trade name Rozerem is	June 21, 2005	Dr. Culley, Mahmud, Toyer, and Holquist

Chemistry Review Data Sheet

	acceptable.		
EA	Approved		
Microbiology	N/A		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ___ Yes ___ No If no, explain reason(s) below:

Appears This Way
On Original

The Chemistry Review for NDA 21-782

The Executive Summary

I. Recommendations

- A. Recommendation and Conclusion on Approvability**
All outstanding issues have been resolved. Requested revisions have been made and submitted to the NDA. From CMC perspective, the recommendation is "approval."

- B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable**
None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

See chemistry review # 1 and 2.

The original NDA was dated 21-SEP-2004, and chemistry review #1 with CMC deficiencies was entered into DFS on 10 June 2005. Amendment 18, dated 22 June 2005, was submitted in response to the Agency communication dated 10 June 2005. Chemistry review #2 was completed on 29 June 2005, with the overall cGMP compliance as acceptable to the Office of Compliance on 11 July 2005.

The Ramelteon drug substance is manufactured from the []
[] at Takeda-Japan (CFN# []). The batch size is []

[] is manufactured from [] []
(CFN# []) The batch size is [] starting material is made from []
[] under contract at [] The batch size is [] There is
no comparability protocol for [] at the time of change of supplier from []
Fate of potential impurities in [] was justified with impurity [] experiments in
API [] There is significant analytical information on []
batches of API to justify process capability to produce [] pure API.

Ramelteon is an indenofuran NME with high affinity and selectivity for human melatonin receptors (MT1 and MT2). Ramelteon has one chiral center, and the (S) form was developed since this form is about [] times more potent at the MT1 receptor than the []
[] ADME studies with C-14 radiotaged Ramelteon has shown very little parent drug. Ramelteon is highly soluble in aqueous solutions and readily partitions into octanol,



Chemistry Assessment Section

thus justifying its cell permeability and long duration of action (once daily). Ramelteon is not hygroscopic, is unable to support microbial burden, has no known polymorphs, and is stable under normal storage conditions when protected from light. Ramelteon undergoes

[

]

The Ramelteon **drug product** is a film coated tablet of 8 mg manufactured at Takeda-Ireland (CFN# 9616691). The batch size is [] tablets. Ramelteon tablet 8mg is a conventional dosage form with no novel excipients. Core tablet weight is 130 mg, and the film coated tablet weight is 135mg. Compendial grade inactive ingredients are used. [] and not in USP. Iron oxide in printing ink complies with 21 CFR 73.1200. Takeda has certified that lactose monohydrate diluent is sourced from [] for human consumption and that magnesium stearate is of [] grade. Immediate release oral tablet design was chosen based on high solubility and oral absorption for Ramelteon. The manufacturing method is a conventional []

]

**Chemistry Assessment Section**

The submitted stability data supports 24 month expiry date based on Q1E decision tree (no significant change at accelerated storage condition within 6 months, long term data shows little or no change over time, shelf life up to 3-times the period covered by long term data but not exceeding 36 months is backed by statistical analysis). 24 months expiry date is also supported with the clinical study period from first subject screened/mfg date to last study subject completed. Stability data does not support the requested 36 months expiration date. Labeling is acceptable, and container labels are qualified with manufactured by and marketed by statements, and without "Best Before" statement.

All associated DMFs are acceptable. The overall Compliance is acceptable as per EES dated 11 July 2005. From a CMC perspective the application is approved.

B. Description of How the Drug Product is intended to be used

See chemistry reviews # 1 .

C. Basis for Approvability or Not-Approval Recommendation

Approved with 24 months expiration date.

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

Dr. Pramod Maturu, PhD, Review Chemist
Dr. Ravi Harapanhalli, PhD, Chemistry Team Leader

C. CC Block

File: NDA 21782_21July2005

7 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

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this page is the manifestation of the electronic signature.**

/s/

Pat Maturu
7/22/05 03:26:53 PM
CHEMIST

Ravi Harapanhalli
7/22/05 03:31:17 PM
CHEMIST



NDA 21-782
Ramelteon Tablets, 8mg.

Takeda Global Research & Development Center Inc. (TGRD)

Chemistry review # 2 by
Dr. Pramoda Maturu, PhD, MBA, HFD-820, for
Division of Anesthetic, Critical Care & Addiction Drug Products
(DACCAD)

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B. Description of How the Drug Product is Intended to be Used.....	7
C. Basis for Approvability or Not-Approval Recommendation.....	7
III. Administrative.....	
A. Reviewer's Signature.....	8
B. Endorsement Block.....	8
C. CC Block	8
Chemistry Assessment.....	
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	
S DRUG SUBSTANCE [Name, Manufacturer].....	Chem Rev # 1
P DRUG PRODUCT [Name, Dosage form].....	Chem Rev #1
A APPENDICES	Chem Rev #1
R REGIONAL INFORMATION	Chem Rev #1
Review Of Common Technical Document-Quality (Ctd-Q) Module 1	
A. Labeling & Package Insert	Chem Rev #1
B. Environmental Assessment Or Claim Of Categorical Exclusion	Chem Rev #1
II. Deficiencies Communicated, responses submitted, and response evaluation	9 to 61
III Deficiencies to be communicated	62



Chemistry Review Data Sheet

1. NDA 21-782
2. REVIEW #: 2
3. REVIEW DATE: 27 June 2005
4. REVIEWER: Dr. Pramoda Maturu, PhD, MBA
5. PREVIOUS DOCUMENTS:

<u>Documents</u>	<u>Document Date</u>
Chemistry Review # 1	10 June 2005
CMC deficiencies communication	10 June 2005

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment 018 (Response to the Agency communication dated 10 June 2005)	22 June 2005

7. NAME & ADDRESS OF APPLICANT:

Name: Takeda Global Research & Development Center
(TGRD)

Address: 475 Half Day Road, Lincolnshire, IL 60069

Representative: Mr. Steve Danielson

Telephone: 847-383-3179

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: [] has rejected this name as acknowledged by the sponsor in the amendment 014 dated 21 April 05)
- b) Non-Proprietary Name (USAN) Ramelteon
- c) Code Name/# (ONDC only) TAK-375, T99375, CAS# 196597-26-9
- d) Chem. Type/Submission Priority (ONDC only):

CHEMISTRY REVIEW

Chemistry Review Data Sheet

- Chem. Type **1**
- Submission Priority **S**

9. LEGAL BASIS FOR SUBMISSION: FDC Act, 21 CFR 314.50, and 505(b)(1)

10. PHARMACOL. CATEGORY: Once daily treatment for insomnia.

11. DOSAGE FORM: Code 502 or 504; Pale orange yellow color film coated round and biconvex tablet with \square and "8" printed on one side. LNC has rejected this name as acknowledged by the sponsor in the amendment 014 dated 21 April 05

12. STRENGTH/POTENCY: 8 mg

13. ROUTE OF ADMINISTRATION: Code 001; orally taken within 30 min prior to bedtime with or without food.

14. Rx/OTC DISPENSED: Rx OTC

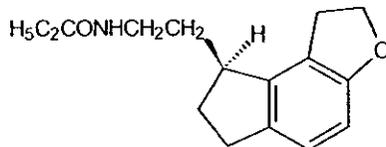
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Ramelteon, TAK-375, is an orally active sleep-promoting agent that is chemically designated as (*S*)-*N*-[2-(1,6,7,8-tetrahydro-2*H*-indeno-[5,4-*b*]furan-8-yl)ethyl]propionamide and contains one chiral center. The submission being reviewed is for the (*S*)-enantiomer, with an empirical formula of $C_{16}H_{21}NO_2$, molecular weight of 259.34, and the following chemical structure:



\square

J



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Each tablet includes the following inactive ingredients: lactose monohydrate, starch, hydroxypropyl cellulose, magnesium stearate, hypromellose, copovidone, titanium dioxide, yellow ferric oxide, polyethylene glycol 8000, and ink containing shellac and synthetic iron oxide black.

17. RELATED/SUPPORTING DOCUMENTS: IND 58,136 and J.Med.Chem. 2002, 45, 4222

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
	II			1	Adequate	3 June 2005 Pramod Maturu	/
	III			1	Adequate	5 Aug 2004 Sarah Pope	Currently marketed
	III			1	Adequate	13 Jun 2002 Jila Boal	Currently marketed
	III			1	Adequate	6 Jan 2005 Rapti Madurawe	Currently marketed
	III			1	Adequate	12 Jan 2005 Rapti Madurawe	Currently marketed
	III			1	Adequate	12 Jan 2004 Monica Cooper	Currently marketed
	III			1	Adequate	3 Mar 2005 Alan Schroeder	Currently marketed
	III			1	Adequate	25 Sep 2002 Gil Jong Kang	Currently marketed

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

CHEMISTRY REVIEW

Chemistry Review Data Sheet

- 3 – Reviewed previously and no revision since last review
- 4 – Sufficient information in application
- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	~ months expiration date (30s and ~ packages for assay)	June 7, 2005	Dr. Buenconsejo, PhD
EES	Pending as of 27 June 2005		
Pharm/Tox	Approved with phase IV commitments	June 22, 2005	Dr. Wasserman, PhD
Biopharm	Acceptable with labeling revisions (food effect)	June 21, 2005	Dr. Lee, PhD
LNC	Proprietary name is pending as of 27 June 2005.		
Methods Validation	Not requested; The Methods are conventional and do not qualify for any of the ONDC interim criteria for MV.		
OPDRA			
EA			
Microbiology			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ___ Yes ___ No If no, explain reason(s) below:



The Chemistry Review for NDA 21-782

The Executive Summary

I. Recommendations

- A. **Recommendation and Conclusion on Approvability**
Approvable, pending acceptable recommendations from the Office of Compliance.
- B. **Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable**

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

See chemistry review # 1 dated 10 June 2005.

B. Description of How the Drug Product is intended to be used

See chemistry review # 1 dated 10 June 2005.

C. Basis for Approvability or Not-Approval Recommendation

Approvable, pending acceptable recommendations from the Office of Compliance. [] pure Ramelteon API was tested in preclinical and clinical studies. There is significant amount of analytical information on ~ batches of API to justify the process capability to produce [] pure API. The Agency has proposed a dissolution spec Q of [] at ~ min for stability for Ramelteon tablets 8mg at the "Industry Meeting dated 15th December 2003", which the applicant is unable to comply. The agency has agreed to relax the dissolution time point to 30 min based on — for batches used in clinical studies for insomnia, which the applicant can meet. There is significant amount of stability data on 3 pilot batches and 3 commercial scale batches of Ramelteon tablets 8mg to justify — months interim expiration date based on statistical analysis (Dr. Buencosejo). The requested — months expiration date can not be currently supported due to low assay values [] at —months time point for one commercial scale batch [] and it will be revisited upon completion of — months test point in Aug 2005.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Dr. Pramod Maturu, PhD, Review Chemist

Dr. Ravi Harapanhalli, PhD, Chemistry Team Leader

C. CC Block

File: NDA 21782_27June05

51 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

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/s/

Pat Maturu
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CHEMIST

Blair Fraser
6/29/05 03:35:42 PM
CHEMIST
Blair A. Fraser, Ph.D., for Ravi Harapanhalli, Ph.D.



NDA 21-782
Ramelteon Tablets, 8mg.

Takeda Global Research & Development Center Inc. (TGRD)

Chemistry review by
Dr. Pramoda Maturu, PhD, MBA, HFD-820, for
Division of Anesthetic, Critical Care & Addiction Drug Products
(DACCAD)



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Chemistry Review Data Sheet

1. NDA 21-782
2. REVIEW #: 1
3. REVIEW DATE: Revised 10 June 2005
4. REVIEWER: Dr. Pramoda Maturu, PhD, MBA
5. PREVIOUS DOCUMENTS:

DocumentsDocument Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Original submission #000
Response to FDA Request
Amendment 011
Amendment 014

21 Sep 2004
14 Jan 2005
23 March 2005
21 April 2005

7. NAME & ADDRESS OF APPLICANT:

Name: Takeda Global Research & Development Center
(TGRD)

Address: 475 Half Day Road, Lincolnshire, IL 60069

Representative: Mr. Steve Danielson

Telephone: 847-383-3179

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: has rejected this name as
acknowledged by the sponsor in the amendment 014 dated 21 April 05)

b) Non-Proprietary Name (USAN) Ramelteon

CHEMISTRY REVIEW

Chemistry Review Data Sheet

c) Code Name/# (ONDC only) TAK-375, T99375, CAS# 196597-26-9

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type 1
- Submission Priority S

9. LEGAL BASIS FOR SUBMISSION: FDC Act, 21 CFR 314.50, and 505(b)(1)

10. PHARMACOL. CATEGORY: Once daily treatment for insomnia.

11. DOSAGE FORM: Code 502 or 504; Pale orange yellow color film coated round and biconvex tablet with \mathcal{L} \mathcal{J} and "8" printed on one side. LNC has rejected this name as acknowledged by the sponsor in the amendment 014 dated 21 April 05

12. STRENGTH/POTENCY: 8 mg

13. ROUTE OF ADMINISTRATION: Code 001; orally taken within 30 min prior to bedtime with or without food.

14. Rx/OTC DISPENSED: Rx OTC

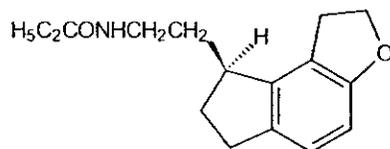
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Ramelteon, TAK-375, is an orally active sleep-promoting agent that is chemically designated as (*S*)-*N*-[2-(1,6,7,8-tetrahydro-2*H*-indeno-[5,4-*b*]furan-8-yl)ethyl]propionamide and contains one chiral center. The submission being reviewed is for the (*S*)-enantiomer, with an empirical formula of $C_{16}H_{21}NO_2$, molecular weight of 259.34, and the following chemical structure:





CHEMISTRY REVIEW



Chemistry Review Data Sheet

Ramelteon is not hygroscopic [] and it has no known polymorphs. [] 1. Ramelteon has []

Each tablet includes the following inactive ingredients: lactose monohydrate, starch, hydroxypropyl cellulose, magnesium stearate, hypromellose, copovidone, titanium dioxide, yellow ferric oxide, polyethylene glycol 8000, and ink containing shellac and synthetic iron oxide black.

17. RELATED/SUPPORTING DOCUMENTS: IND 58,136 and J.Med.Chem. 2002, 45, 4222

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
	II			1	Adequate	3 June 2005 Pramod Maturu	
	III			1	Adequate	5 Aug 2004 Sarah Pope	Currently marketed
	III			1	Adequate	13 Jun 2002 Jila Boal	Currently marketed
	III			1	Adequate	6 Jan 2005 Rapti Madurawe	Currently marketed
	III			1	Adequate	12 Jan 2005 Rapti Madurawe	Currently marketed
	III			1	Adequate	12 Jan 2004 Monica Cooper	Currently marketed
	III			1	Adequate	3 Mar 2005 Alan Schroeder	Currently marketed
	III			1	Adequate	25 Sep 2002 Gil Jong Kang	Currently marketed

¹ Action codes for DMF Table:

CHEMISTRY REVIEW

Chemistry Review Data Sheet

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Pending as of 10 June 2005		
Pharm/Tox			
Biopharm			
LNC	Proprietary name is pending as of 10 June 2005.		
Methods Validation	Not requested; The Methods are conventional and do not qualify for any of the ONDC interim criteria for MV.		
OPDRA			
EA			
Microbiology			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ___ Yes ___ No If no, explain reason(s) below:



The Chemistry Review for NDA 21-782

The Executive Summary

I. Recommendations

- A. **Recommendation and Conclusion on Approvability**
Approvable, pending satisfactory resolution of the deficiencies listed at the end of the review, and upon acceptable recommendations from the Office of Compliance.
- B. **Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable**

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Ramelteon, (S)-N-(2-(1,6,7,8-tetrahydro-2H-indeno(5,4-b)furan-8-yl)ethyl) propionamide, is a novel molecular entity (NME) with high affinity and selectivity for human melatonin receptors (MT1 and MT2) and with negligible affinity for GABA receptors. Ramelteon is a single enantiomer one chiral center drug type NME. Ramelteon affinity to MT1 receptor is stronger than melatonin that is secreted by the pineal gland to control mammalian circadian rhythms that is concurrent with nocturnal sleep. During the drug discovery program, the methoxy group in melatonin is fixed and conformationally restricted with an oxygen atom in the 6-position into a furan, and the sleep inducing action and the duration of sleep effect of Ramelteon is about 10 times greater than for melatonin in cat model. As a result, Ramelteon does not produce side effects associated with GABA receptor binding as shown with Zolpidem (sedation, anxiolysis, muscle relaxation, amnesia). Ramelteon has one chiral center, and the (S) form is developed since this form is about 10 times more potent at MT1 receptor than the (R) form by receptor expression studies with CHO cells. Both, Ramelteon (8mg) and Zolpidem (10mg) are taken orally at bedtime as sleep medicines, and they are from different chemical classes. Ramelteon is an indeno furan class, and Zolpidem is an imidazopyridine class. Ramelteon decreases the time to sleep onset and increases sleep duration. ADME studies with C-14 radiotaged Ramelteon (TAK-375) has shown very little parent drug (0.5% total radioactivity) and M-11 as major metabolite (14.5% total radioactivity), and thus the drug is extensively metabolized. M-II metabolite is hydroxylated class, and it is more polar and early eluting. Ramelteon is a neutral compound with no acid or base functional groups, and as such, its aqueous solubility is independent of pH. Ramelteon is BAS class I with high aqueous solubility and high partition into octanol to justify its cell permeability and long duration of action (once daily). Ramelteon solid is not hygroscopic, it has no known polymorphs, and it is stable under normal storage conditions when protected from light.

C

J



Executive Summary Section

for producing Ramelteon as /batch. The annual demand forecast is from batches. Ramelteon

The analytical laboratory controls for Ramelteon API include

which are the characteristics of Ramelteon. There is no correction to the assay value since the enantiomer content is NMI. The sample preparation for assay is LOQ is for all related compounds. The response factors are for all others. Reported levels for related compounds are very much lower (Mean plus 3 sigma is) than the proposed specifications. There to pose a safety risk. Only was and in the synthesis of Ramelteon. The proposed specification ppm is much tighter than the ICH limit of 720 ppm, and the proposed specification for ppm is based on GMP considerations since there is no upper bound for. Ramelteon is not hygroscopic, there is no moisture to support microbial growth, and as there is no specification for microbial bioburden. The particle size specifications includes based on an observation that Ramelteon tablets made from materials from had shown similar dissolution profiles.

An immediate release (IR) tablet was chosen for Ramelteon based on the high aqueous solubility and oral absorption. The round core tablet contains the active, lactose, starch, hydroxypropylcellulose, magnesium stearate. A procedure was developed for making the tablets and a yellow film coating.

The tablet formulation developed for the original IND 58136 remained essentially the same with minor optimizations.

Phase III clinical formulation tablets is slightly modified by imprinting with printing ink for US marketing., and this additional process step did not effect dissolution profile. Ramelteon 8 mg tablets with printing are manufactured at Takeda-Ireland at tablets per batch size. There is no overage for the active.

The analytical laboratory controls for Ramelteon tablets 8 mg include

in vitro dissolution (Q of at min), and visual check for appearance. Ramelteon is a single enantiomer one chiral center drug type NME but the chiral identity is not in drug product specification. There is data to justify that that minor enantiomer does not increase in drug product. The Agency has proposed a dissolution spec Q of at 15 min for stability at the "Industry Meeting dated 15th December 2003". However, the applicant did not agree and filed the NDA with a dissolution specs Q of. What is an appropriate dissolution spec for a sleep medication is a disputed item that requires a solution.

Q of is a recommendation from the "Dissolution testing IR solid oral dosage form guidance document". However, Q at 15 min is the recommendation from ICH Q6A notice document decision tree# 7. One can also articulate that Q at 15 min for stability is an appropriate drug standard for a sleep medication like Ramelteon tablet 8 mg based on the Agency approved dissolution spec for Zolpidem tartrate tablets 5mg and 10mg (NDA 19-908), which the applicant is not able to meet. Observed Q values for Ramelteon tablets 8mg are in the range



Executive Summary Section

[

]

B. Description of How the Drug Product is intended to be used

The recommended dose is 8 mg taken within 30 minutes prior to bedtime. Ramelteon tablets can be administered with or without food. It is supplied in bottles as 30s, 100s, and 500s, and in blisters. It is stored at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). The bottle is tightly closed to protect tablets from moisture and humidity.

C. Basis for Approvability or Not-Approval Recommendation

Highly pure Ramelteon API was tested in preclinical and clinical studies. There is significant amount of analytical information on batches of API to justify the process capability to produce pure API. However, a less pure Ramelteon API is proposed for US marketing. The Agency has proposed a dissolution spec Q of at min for stability at the "Industry Meeting dated 15th December 2003", which the applicant is unable to comply. When the agency agrees to relax the dissolution time point to min, then the applicant can meet with a shorter shelf life of months.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Dr. Pramod Maturu, PhD, Review Chemist
Dr. Ravi Harapanhalli, PhD, Chemistry Team Leader

C. CC Block

104 Page(s) Withheld

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

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

Withheld Track Number: Chemistry-

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

/s/

Pat Maturu
6/10/05 03:06:16 PM
CHEMIST

Blair Fraser
6/10/05 03:11:44 PM
CHEMIST
Blair A. Fraser, Ph.D., for Ravi Harapanhalli, Ph.D.