

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203794Orig1s000

CHEMISTRY REVIEW(S)

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

DATE: 19-SEP-2012
TO: N203794 File
FROM: Craig M. Bertha, Ph.D.
Chemistry Reviewer
ONDQA, Division III, Branch VIII
THROUGH: Prasad Peri, Ph.D.
Branch Chief
ONDQA, Division III, Branch VIII



SUBJECT: ACCEPTABLE recommendation from the Office of Compliance for application of 18-SEP-2012; Final CMC recommendation

SUMMARY: The Office of Compliance has placed an overall recommendation of ACCEPTABLE into the EES on 18-SEP-2012. The CMC team can now recommend that the application be **approved**.

RECOMMENDATION: The application is recommended for **approval**.

Craig M. Bertha, Ph.D.
Chemist

cc:
OND/DAAAP/DChiapperino
ONDQA/DIV 1/CBertha/19-SEP-2012
ONDQA/DIV 1/PPeri_____
ONDQA/DIV1/DChristodoulou
OND/DAAAP/EFields
ONDQA/LRivera

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/s/

CRAIG M BERTHA
09/19/2012

PRASAD PERI
09/20/2012
I concur

NDA 203794

Nucynta® (tapentadol) Oral Solution

Janssen Pharmaceuticals, Inc.

**Craig M. Bertha, Ph.D.
Office of New Drug Quality Assessment
Division III/Branch VIII**

for

Division of Anesthesia, Analgesia, and Addiction Products

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Chemistry Review Data Sheet

1. NDA 203794
2. REVIEW #: 3
3. REVIEW DATE: 13-AUG-2012
4. REVIEWER: Craig M. Bertha, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

Original
Amendment

Document Date

15-DEC-2011
03-APR-2012 (response to CMC DR)

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Amendment
Amendment (reviewed by microbiology team)
Amendment (reviewed by microbiology team)
Amendment
Amendment
Amendment

Document Date

07-MAY-2012
07-MAY-2012
13-JUN-2012
18-JUN-2012
03-AUG-2012
10-AUG-2012

7. NAME & ADDRESS OF APPLICANT:

Name: Ortho-McNeil-Janssen Pharmaceuticals, Inc.

Chemistry Review Data Sheet

Janssen Research & Development, L.L.C.
920 Route 202 P.O. Box 300
Raritan, NJ 08869

Address: On behalf of
Janssen Pharmaceuticals, Inc.
1125 Trenton-Harbourton Road, P.O. Box 200
Titusville, NJ 08560-0200

Representative: Peggy Ferrone, Manager, Regulatory Affairs

Telephone: 908-704-5116

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Nucynta®
- b) Non-Proprietary Name (USAN): tapentadol
- c) Code Name/# (ONDQA only): R331333, CG5503, BN200, CAS No. 175591-09-0
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: tapentadol is a centrally acting analgesic proposed for the relief of moderate to severe acute pain in patients 18 years of age or older; analgesia is thought to be due to mu-opioid activity and inhibition of norepinephrine uptake

11. DOSAGE FORM: oral solution

12. STRENGTH/POTENCY: 20 mg tapentadol (23.3 tapentadol HCl) per mL of solution

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: X Rx OTC

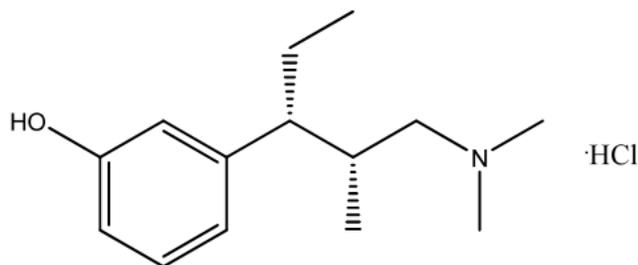
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

Chemistry Review Data Sheet

____ SPOTS product – Form Completed

X Not a SPOTS product

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



Chemical Name: 3-[(1*R*,2*R*)-3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol monohydrochloride
 Molecular formula: C₁₄H₂₃NO·HCl
 Molecular Weight: 257.81 g/mol; Free base: 221.35 g/mol
 CAS: 175591-09-0

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS ³
(b) (4)	3		(b) (4)	3	Adequate	18-APR-2012	(b) (4)
	4		3	Adequate	30-JAN-2012		
	3		4				
	3		4				
	3		4	N/A		No product contact; see P.7 evaluation	
	3		4				
	3		4	N/A		(b) (4)	
	2		3		Adequate	17-JAN-2012	
	3		3,4		Adequate	07-AUG-2012	(b) (4)

Chemistry Review Data Sheet

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)

³ Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
NDA	200533	Janssen Pharmaceuticals, Inc.	Approved 25-AUG-2011; ER tablet
IND	61345	Johnson & Johnson Pharmaceutical R&D, LLC	Active; acute and chronic pain; IR tablet
IND	105766	Johnson & Johnson Pharmaceutical R&D, LLC	Active; neuropathic pain; ER tablets
IND	108134	Johnson & Johnson Pharmaceutical R&D, LLC	Active; oral solution

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics				N/A
EES		17-, 23-JAN-2012 & 06-FEB-2012	Pending	
Pharm/Tox				N/A
ONDQA Biopharm				N/A
LNC				N/A
Methods Validation				N/A
EA				N/A
Microbiology	Microbial limits testing, preservative absence	12-JAN-2012	Final/B. Riley Ph.D.	Recommend approval on the basis of product quality microbiology

The Chemistry Review for NDA 203794

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is considered to be **approvable** as the recommendation from the Office of Compliance is pending.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None at this time.

II. Summary of Chemistry Assessments

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

The drug product is Nucynta® (tapentadol) Oral Solution and it is indicated for the relief of moderate to severe acute pain in patients 18 years of age or older. The drug substance is tapentadol hydrochloride, which is a chiral opioid compound obtained by chemical synthesis (b) (4)

(b) (4) The drug has already been approved for use to treat moderate to severe acute and chronic pain with immediate and extended release solid oral dosage forms, respectively. The (b) (4) form of the drug substance is inconsequential as it is formulated in solution. The drug substance is manufactured for Janssen and information regarding the manufacturer of the drug substance is held in DMF (b) (4).

The drug product is manufactured by (b) (4). The aqueous-based solution formulation contains no co-solvents, has a target pH of 4.0, and also contains both sucralose and a proprietary flavor mixture, for taste purposes. The clear and colorless formulation is simply prepared by (b) (4). The strength of the formulation, in terms of the tapentadol base, is 20 mg/mL (equivalent to 23.3 mg of tapentadol hydrochloride), and the formulation is packaged in quantities of 100 and 200 mL in high density polyethylene bottles fitted with foil induction seals and (b) (4) closures. To ensure accurate dosing, the bottled product is packaged with an oral dosing syringe (b) (4) that includes three gradations corresponding to doses of 50, 75 and 100 mg of tapentadol. This dosing syringe also comes with a bottle adapter which is inserted by the patient into the bottle after removal of the foil induction seal. A 24 month expiration dating period is supported by the stability data that

have been provided in the application and the product is intended to be stored at room temperature.

B. Description of How the Drug Product is Intended to be Used

The drug product packages of 100 and 200 mL of formulation have a concentration of 20 mg/mL and provide 20-40 and 40-80 doses, respectively, corresponding to the labeled doses of 50-100 mg to be taken every 4-6 hours. Daily doses of more than 700 mg the first day and more than 600 mg on subsequent days are not recommended by the applicant in the label.

C. Basis for Approvability or Not-Approval Recommendation

The recommendation from the Office of Compliance for the application is PENDING. Note that the CMC-related labeling comments captured in the first review have not been conveyed to the applicant.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Craig M. Bertha, Ph.D./Chemistry Reviewer: 13-AUG-2012
Prasad Peri, Ph.D./Branch Chief _____

C. CC Block

DChristodoulou/DNDQA III
DChiapperino/DAAAP
KRiviere/ONDQA
DBaugh/OSE/OMEPRM/DMEPA
EFields/DAAAP
AEmami/DAAAP
LRivera/ONDQA
YZhou/OB/DBII
DLee/OCP/DCPII

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/s/

CRAIG M BERTHA
08/14/2012

PRASAD PERI
08/14/2012
I concur

NDA 203794

Nucynta® (tapentadol) Oral Solution

Janssen Pharmaceuticals, Inc.

**Craig M. Bertha, Ph.D.
Office of New Drug Quality Assessment
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I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data	9
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Chemistry Review Data Sheet

1. NDA 203794
2. REVIEW #: 2
3. REVIEW DATE: 24-APR-2012
4. REVIEWER: Craig M. Bertha, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	15-DEC-2011

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Amendment	03-APR-2012 (response to CMC DR)

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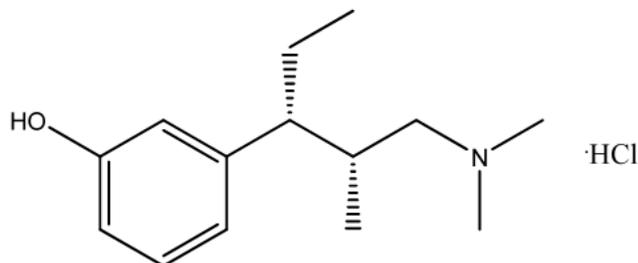
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	3		4				
	3		4	N/A		No product contact; see P.7 evaluation	
	3		4				
	3		4	N/A		No product contact, for inner part of (b) (4)	
	2		3		Adequate	17-JAN-2012	

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Chemistry Review Data Sheet

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EES		17-, 23-JAN-2012 & 06-FEB-2012	Pending	
Pharm/Tox				N/A
ONDQA Biopharm				N/A
LNC				N/A
Methods Validation				N/A
EA				N/A
Microbiology	Microbial limits testing, preservative absence	12-JAN-2012	Interim/S. Langille, Ph.D.	IR letter issued 20-APR-2012

The Chemistry Review for NDA 203794

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is considered to be **approvable** as there are outstanding CMC-related and microbiology issues. Moreover, the facility inspections are outstanding and the above CMC recommendation does not incorporate any potential facility inspection issues. **It is requested that the PM send the microbiology information request to the applicant (see their consult review of 19-APR-2012).**

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None at this time.

II. Summary of Chemistry Assessments

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

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(b) (4) The strength of the formulation, in terms of the tapentadol base, is 20 mg/mL (equivalent to 23.3 mg of tapentadol hydrochloride), and the formulation is packaged in quantities of 100 and 200 mL in high density polyethylene bottles fitted with foil induction seals and (b) (4) closures. To “ensure accurate dosing” the bottled product is packaged with an oral dosing syringe that includes three gradations corresponding to doses of 50, 75 and 100 mg of tapentadol. A 24 month expiration dating period is supported by the stability data that have been provided in the application and the product is intended to be stored at room temperature.

B. Description of How the Drug Product is Intended to be Used

The drug product packages of 100 and 200 mL of formulation have a concentration of 20 mg/mL and provide 20-40 and 40-80 doses, respectively, corresponding to the labeled doses of 50-100 mg to be taken every 4-6 hours. Daily doses of more than 700 mg the first day and more than 600 mg on subsequent days are not recommended by the applicant in the label.

C. Basis for Approvability or Not-Approval Recommendation

There are currently outstanding microbiology issues (IR letter to issue) and the recommendation from the Office of Compliance for the application is PENDING. There is also a CMC-related issue regarding the dosing pipette accuracy. In addition, the CMC-related labeling comments captured in the first review have not been conveyed to the applicant.

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

Craig M. Bertha, Ph.D./Chemistry Reviewer: 24-APR-2012
Prasad Peri, Ph.D./Branch Chief _____

C. CC Block

DChristodoulou/DNDQA I
DChiapperino/DAAAP
KRiviere/ONDQA
DBaugh/OSE/OMEPRM/DMEPA
EFields/DAAAP
AEmami/DAAAP
KSharma/ONDQA
YZhou/OB/DBII
DLee/OCP/DCPII

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/s/

CRAIG M BERTHA
04/24/2012

PRASAD PERI
04/25/2012
I concur

MEMORANDUM

Date: February 24, 2012

To: NDA 203794

From: Christine M. V. Moore, Ph.D.
Acting Office Director
ONDQA

Subject: ONDQA recommendation on biowaiver for NDA 203794 Nucynta Oral Solution

This memo relates to the suitability of a biowaiver for NDA 203794 Nucynta Oral Solution relative to the immediate release tablet. I have reviewed the current and previous review documents and related research literature on this matter, and have held meetings with the primary reviewer (Dr. Kareen Riviere), the secondary reviewer (Dr. Sandra Suarez-Sharp), and the Acting Biopharm Supervisor (Dr. Angelica Dorantes) to discuss the issues related to the suitability of the biowaiver. I believe that I have a good understanding of the data available and the regulatory requirements. Based on the information reviewed, I deem that the biowaiver granted by ONDQA for IND 61,345 on 6/29/09 is valid for NDA 203794.

Background:

Tapentadol is a highly soluble, highly permeable drug that was granted BCS-1 classification by the CDER BCS Committee in September 2008. Immediate release Tapentadol tablets were approved by FDA on 11/20/08 for the relief of moderate to severe acute pain in adults. In 2009, the applicant requested a biowaiver for an oral solution of tapentadol with two strengths (4 mg/ml and 20 mg/ml) relative to the approved immediate tablet. The biowaiver was granted on 6/29/09. The 20 mg/ml formulation utilized in NDA 203794 is identical to that previously granted a biowaiver in IND 61,345.

Current Issue:

In the ONDQA Biopharmaceutics Filing Review, the reviewer determined that the previously approved biowaiver was not valid for the proposed 20 mg/ml tapentadol oral solution. The reviewer states that per the BCS guidance for industry, demonstration in vivo BA or BE data may not be necessary for pharmaceutically equivalent drug products containing Class 1 drug substances, as long as the active ingredients do not significantly affect absorption of the active ingredients. The reviewer believes that the current drug product does not meet this requirement because:

- The proposed product and the reference product do not meet the definition of pharmaceutical equivalents in 21 CFR 320.1 because they are not the same dosage form.
- The proposed product contains sucralose as an inactive ingredient which may affect bioavailability.

I do not find either of these arguments compelling enough to overturn the previous decision to grant a biowaiver.

Related to the first point, this matter is deemed to be a difference in interpretation of regulations and guidance. Neither the regulatory requirements in the CFR nor the related guidance for biowaivers have changed since the biowaiver was granted in 2009. While biowaivers for a solution with a BCS 1 component is not explicitly discussed in the regulations, it is consistent with CDER's Guidance on *Bioavailability and Bioequivalence for Orally Administered Products – General Considerations* which states “Generally, in vivo BE studies are waived for solutions on the assumption that release of the drug substance from the drug product is self evident and that the solutions do not contain any excipients that significantly affect drug absorption (21 CFR 320.22(b)(3)(iii).”

Regarding the second point, I find a negligible risk that the sucralose in the formulation could affect bioavailability. While the cited paper (Abou-Donia, et. al 2008) provides information that sucralose can affect expression levels of certain enzymes transporters that could affect bioavailability of some drugs, it should be noted that this study was performed in animal models over an 12 week period of time. The product under consideration is intended for acute pain indication and the concentration of sucralose (approximately (b) (4)) lower than the lowest concentration studied in the paper. Furthermore, the cited work has been refuted by later authors ((b) (4)). Finally, the total amount of sucralose in the formulation is quite low compared to other food products; a 100 mg tapentadol dose contains (b) (4) of sucralose, approximately equal to one packet of commercially available sweetener.

Recommendation:

After reviewing the available information and discussing the issues with Drs. Riviere, Suarez-Sharp and Dorantes, insufficient evidence was found to present reverse the biowaiver granted on the same formulation on 6/29/09. Consequently, the ONDQA recommendation is that the biowaiver be considered valid for NDA 203794. While this decision does not impact the ONDQA review of the application, it may affect the Office of Clinical Pharmacology review approach.

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/s/

CHRISTINE M MOORE
02/24/2012

NDA 203794

Nucynta® (tapentadol) Oral Solution

Janssen Pharmaceuticals, Inc.

**Craig M. Bertha, Ph.D.
Office of New Drug Quality Assessment
Division III/Branch VIII**

for

Division of Anesthesia, Analgesia, and Addiction Products

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Chemistry Review Data Sheet

1. NDA 203794
2. REVIEW #:1
3. REVIEW DATE: 09-FEB-2012
4. REVIEWER: Craig M. Bertha, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

15-DEC-2011

Original

7. NAME & ADDRESS OF APPLICANT:

Name: Ortho-McNeil-Janssen Pharmaceuticals, Inc.
Janssen Research & Development, L.L.C.
920 Route 202 P.O. Box 300
Raritan, NJ 08869

Address: On behalf of
Janssen Pharmaceuticals, Inc.
1125 Trenton-Harbourton Road, P.O. Box 200
Titusville, NJ 08560-0200

Representative: Peggy Ferrone, Manager, Regulatory Affairs

Telephone: 908-704-5116

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

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- b) Non-Proprietary Name (USAN): tapentadol
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- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: analgesic; tapentadol is a centrally acting opioid compound and is proposed for the relief of moderate to severe acute pain in patients 18 years of age or older

11. DOSAGE FORM: oral solution

12. STRENGTH/POTENCY: 20 mg tapentadol (23.3 tapentadol HCl) per mL of solution

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: Rx OTC

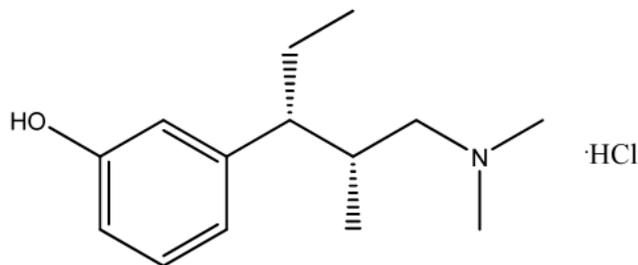
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product – Form Completed

Not a SPOTS product

Chemistry Review Data Sheet

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



Chemical Name: 3-[(1*R*,2*R*)-3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol monohydrochloride
 Molecular formula: C₁₄H₂₃NO·HCl
 Molecular Weight: 257.81 g/mol; Free base: 221.35 g/mol
 CAS: 175591-09-0

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS ³
(b) (4)	3	(b) (4)	(b) (4)	7			Applicant has not identified component supplied by holder; see p. 36
	4			3	Adequate	30-JAN-2012	
	3			4			
	3			4			
	3			4	N/A		No product contact; see P.7 evaluation
	3			4			
	3			4	N/A		No product contact, for inner part of (b) (4)
	2			3	Adequate	17-JAN-2012	

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

Chemistry Review Data Sheet

- 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)

³ Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
NDA	200533	Janssen Pharmaceuticals, Inc.	Approved 25-AUG-2011; ER tablet
IND	61345	Johnson & Johnson Pharmaceutical R&D, LLC	Active; acute and chronic pain; IR tablet
IND	105766	Johnson & Johnson Pharmaceutical R&D, LLC	Active; neuropathic pain; ER tablets
IND	108134	Johnson & Johnson Pharmaceutical R&D, LLC	Active; oral solution

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics				N/A
EES		17-, 23-JAN-2012 & 06-FEB-2012	Pending	
Pharm/Tox				N/A
ONDQA Biopharm				N/A
LNC				N/A
Methods Validation				N/A
EA				N/A
Microbiology	Microbial limits testing, preservative absence	12-JAN-2012	Pending	

The Chemistry Review for NDA 203794

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is not recommended for approval until the issues identified in the **draft discipline review letter** are addressed. Also, there is an outstanding consult with the microbiology team in OPS. Moreover, the facility inspections are outstanding and the above CMC recommendation does not incorporate any potential facility inspection issues.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None at this time.

II. Summary of Chemistry Assessments

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

The drug product is Nucynta® (tapentadol) Oral Solution and it is to be indicated for the relief of moderate to severe acute pain in patients 18 years of age or older. The drug substance is tapentadol hydrochloride, which is a chiral opioid compound obtained by chemical synthesis (b) (4). It has already been approved for use to treat moderate to severe acute and chronic pain with immediate and extended release formulations, respectively. The (b) (4) form of the drug substance is unimportant as it is formulated in solution. The aqueous-based solution formulation contains no co-solvents, has a target pH of 4.0, and also contains both sucralose and a proprietary flavor mixture, for taste purposes. The clear and colorless formulation is simply prepared by (b) (4). The strength of the formulation, in terms of the tapentadol base, is 20 mg/mL, and the formulation is packaged in quantities of 100 and 200 mL in high density polyethylene bottles fitted with foil induction seals and (b) (4) closures. To “ensure accurate dosing” the bottled product is packaged with an oral dosing syringe that includes three gradations corresponding to doses of 50, 75 and 100 mg of tapentadol. A 24 month expiration dating period is supported by the stability data that have been provided in the application and the product is intended to be stored at room temperature.

B. Description of How the Drug Product is Intended to be Used

The drug product packages of 100 and 200 mL of formulation have a concentration of 20 mg/mL and provide 20-40 and 40-80 doses, respectively, corresponding to the labeled doses of 50-100 mg to be taken every 4-6 hours. Daily doses of more than 700 mg the first day and more than 600 mg on subsequent days are not recommended by the applicant in the label.

C. Basis for Approvability or Not-Approval Recommendation

The application is not currently recommended for approval. CMC related issues that are currently unresolved are captured in the attached draft discipline review letter. It is expected that the applicant will be able to provide the requested information and data and revise the application such that it will be possible for the CMC team to recommend approval in the future.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Craig M. Bertha, Ph.D./Chemistry Reviewer: 09-FEB-2012
Prasad Peri, Ph.D./Branch Chief _____

C. CC Block

DChristodoulou/CMC Lead
DChiapperino/PM
SSuarez/ONDQA Biopharm.
SPatwardhan/ONDQA PM

36 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

CRAIG M BERTHA
02/14/2012

PRASAD PERI
02/15/2012
I concur