

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

200533Orig1s000

CHEMISTRY REVIEW(S)

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

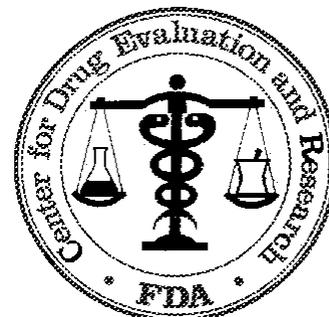
DATE: 25-OCT-2010

TO: N200533 File

FROM: Craig M. Bertha, Ph.D.
Chemistry Reviewer
ONDQA, Division III, Branch VIII

THROUGH: Prasad Peri, Ph.D.
Acting Branch Chief
ONDQA, Division III, Branch VIII

SUBJECT: Updated dissolution acceptance criteria proposed in the 18-OCT-2010, meeting briefing document



SUMMARY: The DAAP sent the applicant a complete response letter dated 01-OCT-2010, for the application. As a result of an evaluation of the IVIVC models and dissolution data, the biopharmaceutics team in ONDQA requested that the applicant revise the dissolution acceptance criteria for the drug product. The purpose of this memorandum is to outline the changes proposed for the drug product dissolution acceptance criteria and how these relate to the dissolution data that have been provided in the application for all strengths of the drug product.

The dissolution specification acceptance criteria that had been proposed in the original application and the newly proposed limits, to be applied to all strengths, are outlined in the table below.

Dissolution Acceptance Criteria (Original) (% release)				
strength/time	30 min	180 min	360 min	600 min
50 mg	(b) (4)			
100 mg				
150 mg				
200 mg				
250 mg				
Newly proposed limits (all strengths)				

Based on the 18 months of 25°C/60%RH stability data that have been provided thus far in the application for the drug product packaged in both the bottles and blisters, it is likely that the dissolution testing will routinely comply with the new acceptance criteria. The following table provides the minimum and maximum individual dissolution results that were observed for the 25°C/60%RH stored drug product in both packaging types.

Minimum and maximum dissolution for bottled and blister packaged drug product on stability over 18 months at 25°C/60%RH												
	Batch/strength/DissTime											
	08G01/50/30	08G07/50/30	08G24/50/30	08G01/50/180	08G07/50/180	08G24/50/180	08G01/50/360	08G07/50/360	08G24/50/360	08G01/50/600	08G07/50/600	08G24/50/600
Min	(b) (4)											
Max												
	08G23/100/30	08G25/100/30	08G29/100/30	08G23/100/180	08G25/100/180	08G29/100/180	08G23/100/360	08G25/100/360	08G29/100/360	08G23/100/600	08G25/100/600	08G29/100/600
Min	(b) (4)											
Max												
	08G31/150/30	08H04/150/30	08H06150/30	08G31/150/180	08H04/150/180	08H06150/180	08G31/150/360	08H04/150/360	08H06150/360	08G31/150/600	08H04/150/600	08H06150/600
Min	(b) (4)											
Max												
	08H20/200/30	08H22/200/30	08H26/200/30	08H20/200/180	08H22/200/180	08H26/200/180	08H20/200/360	08H22/200/360	08H26/200/360	08H20/200/600	08H22/200/600	08H26/200/600
Min	(b) (4)											
Max												
	08G09/250/30	08G17/250/30	08G15/250/30	08G09/250/180	08G17/250/180	08G15/250/180	08G09/250/360	08G17/250/360	08G15/250/360	08G09/250/600	08G17/250/600	08G15/250/600
Min	(b) (4)											
Max												
	30 min			180 min			360 min			600 min		
ranges	(b) (4)											
New AC												

It is also noted that the revised acceptance criteria for the 180 and 360 minute dissolution time-points are no longer (b) (4) i.e., the limit at which point the ICH Q6A guidance would recommend that appropriate bioavailability data be provided to validate the acceptance ranges.

RECOMMENDATION: From a quality control CMC perspective, there is no objection to the changes that have been made to the dissolution acceptance criteria. Ultimately, the final acceptance of the revised acceptance criteria will be dependent upon the evaluation of the biopharmaceutics team.

Craig M. Bertha, Ph.D.
CMC Reviewer, ONDQA

cc:
OND/DAAP/DChiapperino
ONDQA/DIV 3/CBertha/25-OCT-2010
ONDQA/DIV 3/PPeri
ONDQA/DIV3/DChristodoulou
ONDQA/SSuarez Sharp

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
10/25/2010

PRASAD PERI
10/26/2010
I concur

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

DATE: 15-SEP-2009

TO: N200533 File

FROM: Craig M. Bertha, Ph.D.
Chemistry Reviewer
ONDQA, Division III, Branch VIII

THROUGH: Prasad Peri, Ph.D.
Acting Branch Chief
ONDQA, Division III, Branch VIII

SUBJECT: Update on Establishment Evaluation Request for N200533 Nucynta™
(tapentadol) Extended Release Tablets); CMC recommendation



SUMMARY:

The Office of Compliance issued an overall recommendation of **ACCEPTABLE** for the application on 15-SEP-2010.

RECOMMENDATION: As per CMC review #3, the application was considered to be approvable, considering that there was no recommendation from the Office of Compliance, and that there was an outstanding consult on the IVIVC models used for bridging various formulations, and the dissolution method and acceptance criteria.

Although the Office of Compliance has given an **ACCEPTABLE** recommendation for the application, from a biopharmaceutics perspective, there remain deficiencies that were addressed in the review from Dr. S. Suarez Sharp of 20-AUG-2010. See review for complete details, but in summary, the applicant's IVIVC models were not considered to be supportive for bridging of clinical batch formulations to the to-be-marketed formulations. Reconstructed IVIVC models resubmitted by the applicant on 23-JUL-2010, are still unacceptable as they contain terms that have no mechanistic foundation. Also the models that used the individual subject concentrations failed external validation which is considered to be an indication of lack of model robustness. Lastly, the proposed dissolution acceptance criteria were based on the IVIVC models, thus the criteria are in need of revision. Considering these remaining biopharmaceutics issues, the overall CMC recommendation is that the application is **approvable**.

Craig M. Bertha, Ph.D.
CMC Reviewer, ONDQA

cc:

OND/DAAP/DChiapperino

ONDQA/DIV 3/CBertha/15-SEP-2010

ONDQA/DIV 3/PPeri

ONDQA/DIV3/DChristodoulou

ONDQA/SSharp-Suarez

OAP/DAVP/DLee

OND/DPARP/EBrodsky

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200533	ORIG-1	ORTHO MCNEIL JANSSEN PHARMACEUTICA LS INC	TAPENTADOL

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
09/15/2010

PRASAD PERI
09/15/2010
I concur

NDA 200533

Nucynta™ (tapentadol) Extended Release Tablets

Ortho-McNeil-Janssen Pharmaceuticals, Inc.

Craig M. Bertha, Ph.D.
Office of New Drug Quality Assessment/Division I/Branch II

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	7
I. Recommendations.....	7
A. Recommendation and Conclusion on Approvability.....	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
II. Summary of Chemistry Assessments.....	7
A. Description of the Drug Product(s) and Drug Substance(s)	7
B. Description of How the Drug Product is Intended to be Used.....	8
C. Basis for Approvability or Not-Approval Recommendation.....	8
III. Administrative.....	8
A. Reviewer's Signature.....	8
B. Endorsement Block.....	8
C. CC Block.....	8
Chemistry Assessment	9

Chemistry Review Data Sheet

1. NDA 200533
2. REVIEW #: 3
3. REVIEW DATE: 08-MAY-2010
4. REVIEWER: Craig M. Bertha, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

30-NOV-2009
11-MAR-2010

Document Date

Original
Amendment

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

30-APR-2010

Document Date

Amendment

7. NAME & ADDRESS OF APPLICANT:

Name: Ortho-McNeil-Janssen Pharmaceuticals, Inc.

Johnson & Johnson Pharmaceutical Research &
Development, L.L.C.
1125 Trenton-Harbourton Road, P.O. Box 200
Titusville, NJ 08560-0200

Address:

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

Representative: Kathleen F. Dusek, RPh, RAC, Assoc. Director, Reg. Affairs

Chemistry Review Data Sheet

Telephone: 609-730-2719

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: analgesic; tapentadol is a centrally acting opioid compound and is proposed for the treatment of chronic pain

11. DOSAGE FORM: extended release tablets

12. STRENGTH/POTENCY: 50, 100, 150, 200, and 250 mg tapentadol (as free base)/tablet

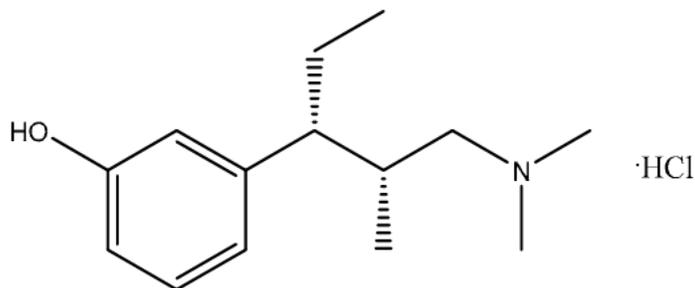
13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: X Rx OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)
 SPOTS product – Form Completed
 X 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: 257.80 g/mol; Free base: 221.34 g/mol
CAS: 175591-09-0

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED (b) (4)	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS ³
				1	Adequate	22-DEC-2009	
				4	Adequate	N/A	These two inks and the film coating system are listed in the Inactive Ingredient Guide as being used in other approved drug products.
				4			
				4			
				4			
				4			
				4			
				4			
				4			
21084	2	Janssen Pharmaceutica, N.V.	Tapentadol HCl (R331333 Drug Substance	3	Adequate	09-APR-2008	Reviewed for N22304 (Nucynta Tablets)

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	22304	Ortho-McNeil-Janssen	NDA for immediate release Nucynta (tapentadol) Tablets for treatment of moderate to severe pain
IND	61345	Ortho-McNeil-Janssen	treatment of moderate to severe pain

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics				N/A
EES		17-DEC-2009	Pending	
Pharm/Tox				N/A
ONDQA Biopharm	IVIVC and dissolution acceptance criteria	10-DEC-2009	Pending/S. Saurez, Ph.D.	
LNC				N/A
Methods Validation				N/A – See p. 91 of CR#1
OPDRA				N/A
EA				N/A – See p. 95 of CR#1
Microbiology				N/A

The Chemistry Review for NDA 200533

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is considered **approvable**, as there is an outstanding consult for the IVIVC and dissolution method/acceptance criteria with the biopharmaceutics team in ONDQA. Also note that 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, Nucynta ER (tapentadol) Extended Release Tablets is a solid dosage form with strengths of 50, 100, 150, 200, and 250 mg (as tapentadol free-base), intended for oral administration. It is indicated for the treatment of chronic pain, and is packaged in high-density polyethylene bottles fitted with child resistant closures, each containing 60 tablets (for all strengths). Each strength is also packaged in cartons, said to be for hospital use only, that contain ten blister cards each containing ten tablets (100 count). The drug product formulation consists of tapentadol hydrochloride (b) (4) polyethylene oxide (b) (4) hypromellose (b) (4) and polyethylene glycol (b) (4). The formulation also contains a small amount (b) (4) of Vitamin E (b) (4). The formulations are not compositionally proportional with respect to the active and excipient components. (b) (4)

(b) (4) The tablet cores are coated with proprietary coatings of different colors for each strength and each is also imprinted with a unique alphanumeric code. It is important to note that the commercial products (tamper-resistant formulations, TRF), described above, differ from that which were studied in the phase 3 clinical trials (PR2 formulations). The applicant is using a BA/BE and IVIVC approach to link the formulations.

The drug substance, tapentadol hydrochloride, is a chiral opioid compound obtained by chemical synthesis (b) (4)

(b) (4) It has already been approved for use to treat moderate to severe pain in an immediate release formulation from the same applicant. (b) (4)

(b) (4)

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

The labeling indicates that the drug product is to be used by patients 18 years of age or older for the management of moderate to severe chronic pain. The product is an opioid analgesic that is to be used around-the-clock for an extended period of time. The daily dose is said to be 100 to 250 mg twice daily (taken at 12 hour intervals), with or without food. Note the 50 mg strength is used for opioid-naïve patients. There are no unusual storage conditions recommended in the labeling and the stability data do not suggest that any such conditions are necessary. The label does indicate that patients should protect the drug product from moisture. Currently the applicant proposes a 24 month expiration dating period for the drug product in both the bottle and blister packaging presentations. The currently available stability data support 24 month expiry periods for both the bottled and blister packaged product.

C. Basis for Approvability or Not-Approval Recommendation

N/A

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Craig M. Bertha, Ph.D./Chemistry Reviewer: 08-MAY-2010
Prasad Peri, Ph.D./Acting Branch Chief _____

C. CC Block

DChristodoulou/PAL
DChiapperino/PM

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200533	ORIG-1	ORTHO MCNEIL JANSSEN PHARMACEUTICA LS INC	TAPENTADOL

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
05/06/2010

PRASAD PERI
05/06/2010
I concur

NDA 200533

Nucynta™ (tapentadol) Extended Release Tablets

Ortho-McNeil-Janssen Pharmaceuticals, Inc.

Craig M. Bertha, Ph.D.
Office of New Drug Quality Assessment/Division I/Branch II

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	7
I. Recommendations.....	7
A. Recommendation and Conclusion on Approvability.....	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
II. Summary of Chemistry Assessments.....	7
A. Description of the Drug Product(s) and Drug Substance(s)	7
B. Description of How the Drug Product is Intended to be Used.....	8
C. Basis for Approvability or Not-Approval Recommendation.....	8
III. Administrative.....	8
A. Reviewer's Signature.....	8
B. Endorsement Block.....	8
C. CC Block.....	8
Chemistry Assessment	9

Chemistry Review Data Sheet

1. NDA 200533
2. REVIEW #: 2
3. REVIEW DATE: 18-MAR-2010
4. REVIEWER: Craig M. Bertha, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
30-NOV-2009	Original

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
11-MAR-2010	Amendment

7. NAME & ADDRESS OF APPLICANT:

Name: Ortho-McNeil-Janssen Pharmaceuticals, Inc.
Johnson & Johnson Pharmaceutical Research &
Development, L.L.C.
1125 Trenton-Harbourton Road, P.O. Box 200
Titusville, NJ 08560-0200

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

Representative: Kathleen F. Dusek, RPh, RAC, Assoc. Director, Reg. Affairs

Telephone: 609-730-2719

Chemistry Review Data Sheet

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: analgesic; tapentadol is a centrally acting opioid compound and is proposed for the treatment of chronic pain

11. DOSAGE FORM: extended release tablets

12. STRENGTH/POTENCY: 50, 100, 150, 200, and 250 mg tapentadol (as free base)/tablet

13. ROUTE OF ADMINISTRATION: oral

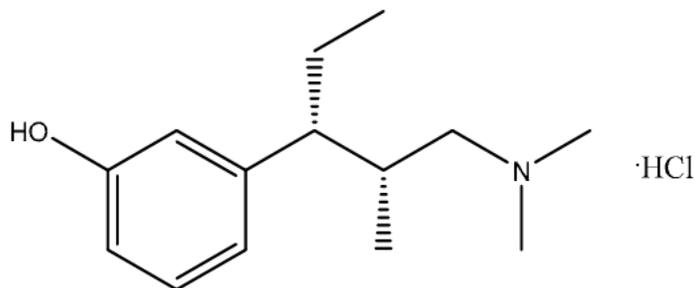
14. Rx/OTC DISPENSED: Rx OTC

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: 257.80 g/mol; Free base: 221.34 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)				1	Adequate	22-DEC-2009	
				4	Adequate	N/A	These two inks and the film coating system are listed in the Inactive Ingredient Guide as being used in other approved drug products.
				4			
				4			
				4			
				4			
				4			
				4			
				4			
				4			
21084	2	Janssen Pharmaceutica, N.V.	Tapentadol HCl (R331333 Drug Substance	3	Adequate	09-APR-2008	Reviewed for N22304 (Nucynta Tablets)

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	22304	Ortho-McNeil-Janssen	NDA for immediate release Nucynta (tapentadol) Tablets for treatment of moderate to severe pain
IND	61345	Ortho-McNeil-Janssen	treatment of moderate to severe pain

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics				N/A
EES		17-DEC-2009	Pending	
Pharm/Tox				N/A
ONDQA Biopharm	IVIVC and dissolution acceptance criteria	10-DEC-2009	Pending/S. Saurez, Ph.D.	
LNC				N/A
Methods Validation				N/A – See p. 91 of CR#1
OPDRA				N/A
EA				N/A – See p. 95 of CR#1
Microbiology				N/A

The Chemistry Review for NDA 200533

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for approval, however, the recommendation from the Office of Compliance is pending. In addition, there is an outstanding consult for the IVIVC and dissolution method/acceptance criteria with the biopharmaceutics team in ONDQA. (b) (4)

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, Nucynta ER (tapentadol) Extended Release Tablets is a solid dosage form with strengths of 50, 100, 150, 200, and 250 mg (as tapentadol free-base), intended for oral administration. It is indicated for the treatment of chronic pain, and is packaged in high-density polyethylene bottles fitted with child resistant closures, each containing 60 tablets (for all strengths). Each strength is also packaged in cartons, said to be for hospital use only, that contain ten blister cards each containing ten tablets (100 count). The drug product formulation consists of tapentadol hydrochloride (b) (4) polyethylene oxide (b) (4) hypromellose (b) (4) and polyethylene glycol (b) (4). The formulation also contains a small amount (b) (4) of Vitamin E (b) (4). The formulations are not compositionally proportional with respect to the active and excipient components. (b) (4)

The tablet cores are coated with proprietary coatings of different colors for each strength and each is also imprinted with a unique alphanumeric code. It is important to note that the commercial product (tamper-resistant formulations, TRF), described above, differs from that which was studied in the phase 3 clinical trials (PR2 formulations). The applicant is using a BA/BE approach to link the formulations.

The drug substance, tapentadol hydrochloride, is a chiral opioid compound obtained by chemical synthesis (b) (4)

(b) (4) It has already been approved for use to treat moderate to severe pain in an immediate release formulation from the same applicant. (b) (4)

(b) (4)

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

The labeling indicates that the drug product is to be used by patients 18 years of age or older for the management of moderate to severe chronic pain. The product is an opioid analgesic that is to be used around-the-clock for an extended period of time. The daily dose is said to be 100 to 250 mg twice daily (taken at 12 hour intervals), with or without food. As such, it is unclear why the application includes a 50 mg strength dosage form. There are no unusual storage conditions recommended in the labeling and the stability data do not suggest that any such conditions are necessary. The label does indicate that patients should protect the drug product from moisture. Currently the applicant proposes a 24 month expiration dating period for the drug product in both the bottle and blister packaging presentations. The currently available stability data, along with the statistical analyses provided for the moisture content stability data for blister packaged drug product (see response to comment 21 in this review), support 24 month expiry periods for both the bottled and blister packaged product.

C. Basis for Approvability or Not-Approval Recommendation

N/A

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Craig M. Bertha, Ph.D./Chemistry Reviewer: 18-MAR-2010
Prasad Peri, Ph.D./Acting Branch Chief _____

C. CC Block

DChristodoulou/PAL
DChiapperino/PM

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200533	ORIG-1	ORTHO MCNEIL JANSSEN PHARMACEUTICA LS INC	TAPENTADOL

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
03/18/2010

PRASAD PERI
03/18/2010
I concur

NDA 200533

Nucynta™ (tapentadol) Extended Release Tablets

Ortho-McNeil-Janssen Pharmaceuticals, Inc.

Craig M. Bertha, Ph.D.

Office of New Drug Quality Assessment/Division I/Branch II

for

**Division of Anesthetics, Analgesics, and Rheumatoid
Products**

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	4
The Executive Summary	9
I. Recommendations.....	9
A. Recommendation and Conclusion on Approvability.....	9
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	9
II. Summary of Chemistry Assessments.....	9
A. Description of the Drug Product(s) and Drug Substance(s)	9
B. Description of How the Drug Product is Intended to be Used.....	10
C. Basis for Approvability or Not-Approval Recommendation.....	10
III. Administrative.....	10
A. Reviewer's Signature.....	10
B. Endorsement Block.....	10
C. CC Block.....	10
Chemistry Assessment	11
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data	11
S DRUG SUBSTANCE [tapentadol HCl, Janssen]	11
P DRUG PRODUCT [tapentadol extended release tablets].....	12
P.1 Description and Composition of the Drug Product [tapentadol extended release tablets].....	12
P.2 Pharmaceutical Development [tapentadol extended release tablets].....	14
P.3 Manufacture [tapentadol extended release tablets]	35
P.4 Control of Excipients [tapentadol extended release tablets]	40
P.5 Control of Drug Product [tapentadol extended release tablets].....	43
P.6 Reference Standards or Materials [tapentadol extended release tablets]	68
P.7 Container Closure System [tapentadol extended release tablets].....	68

P.8 Stability [tapentadol extended release tablets]	72
A APPENDICES	91
A.1 Facilities and Equipment (biotech only).....	91
A.2 Adventitious Agents Safety Evaluation.....	91
A.3 Novel Excipients	91
R REGIONAL INFORMATION	92
R1 Executed Batch Records	92
R2 Comparability Protocols	92
R3 Methods Validation Package	92
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1.....	93
A. Labeling & Package Insert	93
B. Environmental Assessment Or Claim Of Categorical Exclusion	94

Chemistry Review Data Sheet

1. NDA 200533
2. REVIEW #:1
3. REVIEW DATE: 21-JAN-2010
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

30-NOV-2009

Original

7. NAME & ADDRESS OF APPLICANT:

Name: Ortho-McNeil-Janssen Pharmaceuticals, Inc.

Johnson & Johnson Pharmaceutical Research &
Development, L.L.C.

1125 Trenton-Harbourton Road, P.O. Box 200
Titusville, NJ 08560-0200

Address:

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

Representative: Kathleen F. Dusek, RPh, RAC, Assoc. Director, Reg. Affairs

Chemistry Review Data Sheet

Telephone: 609-730-2719

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: analgesic; tapentadol is a centrally acting opioid compound and is proposed for the treatment of chronic pain

11. DOSAGE FORM: extended release tablets

12. STRENGTH/POTENCY: 50, 100, 150, 200, and 250 mg tapentadol (as free base)/tablet

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: X Rx OTC

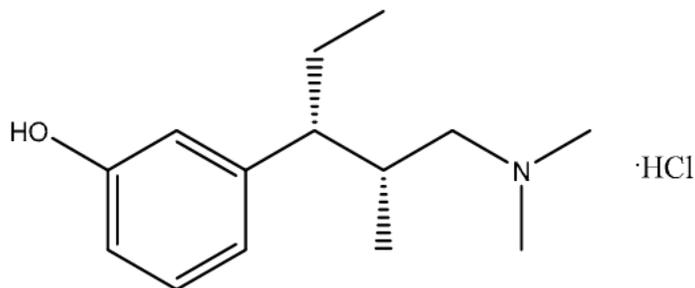
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

 SPOTS product – Form Completed

 X 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: 257.80 g/mol; Free base: 221.34 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)	1	Adequate	22-DEC-2009	
				4	Adequate	N/A	These two inks and the film coating system are listed in the Inactive Ingredient Guide as being used in other approved drug products.
				4			
				4			
				4			
				4			
				4			Applicant will be asked to affirm that they are assuring the correct type of foil is used (see deficiency on p. 72)
				4			
				4			

Chemistry Review Data Sheet

		(b) (4)					
21084	2	Janssen Pharmaceutica, N.V.	Tapentadol HCl (R331333 Drug Substance	3	Adequate	09-APR-2008	Reviewed for N22304 (Nucynta Tablets)

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	22304	Ortho-McNeil-Janssen	NDA for immediate release Nucynta (tapentadol) Tablets for treatment of moderate to severe pain
IND	61345	Ortho-McNeil-Janssen	treatment of moderate to severe pain

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics				N/A
EES		17-DEC-2009	Pending	
Pharm/Tox				N/A
ONDQA Biopharm	IVIVC and dissolution acceptance criteria	10-DEC-2009	Pending/S. Saurez, Ph.D.	
LNC				N/A
Methods Validation				N/A – See p. 92
OPDRA				N/A



CHEMISTRY REVIEW



Chemistry Review Data Sheet

EA				N/A – See p. 96
Microbiology				N/A

The Chemistry Review for NDA 200533

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is considered **approvable** from the CMC perspective. **It is requested that the project manager forward the comments in the attached draft discipline review letter to the applicant.**

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, Nucynta ER (tapentadol) Extended Release Tablets is a solid dosage form with strengths of 50, 100, 150, 200, and 250 mg (as tapentadol free-base), intended for oral administration. It is indicated for the treatment of chronic pain, and is packaged in high-density polyethylene bottles fitted with child resistant closures, each containing 60 tablets (for all strengths). Each strength is also packaged in cartons, said to be for hospital use only, that contain ten blister cards each containing ten tablets (100 count). The drug product formulation consists of tapentadol hydrochloride (b) (4) polyethylene oxide (b) (4) hypromellose (b) (4) and polyethylene glycol (b) (4). The formulation also contains a small amount (b) (4) of Vitamin E (b) (4). The formulations are not compositionally proportional with respect to the active and excipient components. (b) (4)

(b) (4) The tablet cores are coated with proprietary coatings of different colors for each strength and each is also imprinted with a unique alphanumeric code. It is important to note that the commercial product (tamper-resistant formulations, TRF), described above, differs from that which was studied in the phase 3 clinical trials (PR2 formulations). The applicant is using a BA/BE approach to link the formulations.

The drug substance, tapentadol hydrochloride, is a chiral opioid compound obtained by chemical synthesis (b) (4)

(b) (4) It has already been approved for use to treat moderate to severe pain in an immediate release formulation from the same applicant. (b) (4)

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

The labeling indicates that the drug product is to be used by patients 18 years of age or older for the management of moderate to severe chronic pain. The product is an opioid analgesic that is to be used around-the-clock for an extended period of time. The daily dose is said to be 100 to 250 mg twice daily (taken at 12 hour intervals), with or without food. As such, it is unclear why the application includes a 50 mg strength dosage form. There are no unusual storage conditions recommended in the labeling and the stability data provided thus far do not suggest that any such conditions are necessary. It is noted that the label does indicate that patients should protect the drug product from moisture. Currently the applicant proposes a 24 month expiration dating period for the drug product in both the bottle and blister packaging presentations. Although the current data are likely supportive of a 24 month expiry for the bottled product, it is not clear that the same expiry is supported for the blister packaged drug product. More data are being requested such that a final decision can be made regarding these expiry proposals.

C. Basis for Approvability or Not-Approval Recommendation

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: 21-JAN-2010
Prasad Peri, Ph.D./Acting Branch Chief _____

C. CC Block

DChristodoulou/PAL
DChiapperino/PM

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200533	ORIG-1	ORTHO MCNEIL JANSSEN PHARMACEUTICA LS INC	TAPENTADOL

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
01/21/2010

PRASAD PERI
01/22/2010
I concur