CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-304

CHEMISTRY REVIEW(S)

Tradename
(tapentadol)
Tablet

NDA 22-304

Division Director Review
Chemistry, Manufacturing, and Controls

Applicant: Ortho-McNeil-Janssen Pharmaceuticals, Inc.
Johnson and Johnson Pharmaceutical Research and Development, LLC
1125 Trenton-Harbourton Road
P.O. Box 200
Titusville, NJ 08560-0200

Indication: Relief of moderate to severe pain

Presentation: Film-coated, immediate release, round tablet for oral administration available in three strengths as follows:

- 50 mg tablets are yellow, [ ] nm, "O-M" on one side, "50" on other;
- 75 mg tablets are yellow-orange, [ ] nm, "O-M" on one side, "75" on other;
- 100 mg tablets are orange, [ ] nm, "O-M" on one side, "100" on other;

b(4)

Tablets are packaged in [ ] bottles with child-resistant caps, 100 count, and in [ ] unit dose blister packs of 10 count.

b(4)

EER Status:		Acceptable	25-FEB-2008
Consults:	Pharm/Tox	Adequate	22-SEP-2008
	Biopharm	Adequate	19-SEP-2008
	Environmental Assessment	Adequate	7-JUL-2008
	Methods Validation – Revalidation by Agency not requested.		
Original Submission:			22-JAN-2008
Post-Approval Agreements:			None

Drug Substance:

The drug substance, tapentadol hydrochloride, is a small, synthetic, New Molecular Entity (NME) with an empirical formula of $C_{14}H_{23}NO \cdot HCl$ and a molecular weight of 257.80. Tapentadol HCl

b(4)

b(4)

The proposed regulatory methods are either compendial or were developed and validated for their intended purpose. The primary reference standard for drug substance, manufactured by the commercial process, has been characterized by the proposed regulatory methods as well as additional methods. The impurity and degradation profiles have been investigated.

b(4)

Conclusion: Drug substance is acceptable.

Drug Product:

Tradename (tapentadol HCl) tablets are film-coated, immediate release, round, tablets available in three strengths of 50 mg, 75 mg, and 100 mg of free-base equivalent of the drug substance. Tablets are uniquely colored and labeled on both sides to distinguish the various strengths. Tablets are packaged in bottles, at 100 count, and in unit blisters of 10 count. b(4)

b(4)

The tapentadol HCl reference standard for drug product is the same as that for drug substance. The proposed regulatory methods are either compendial or were developed and validated for their intended purpose.

The stability data support an expiration dating of 18 months for all strengths of drug product stored at controlled room temperature conditions [25° C (77° F); excursions permitted to 15-30° C (59-86° F)], and packaged in [ ] bottles and [ ] blisters. b(4)

Conclusion: Drug product is acceptable.

Additional Items:

- The applicant agreed to continue the primary stability studies on the three commercial scale lots of each presentation of drug product to firmly establish the proposed shelf life.
- The sponsor agreed to place on stability the first three commercial production lots of each presentation of drug product of drug product, following the approved stability protocol.
- The sponsor agreed to place on stability at least one commercial production lot of each presentation of drug product, per year, following the approved stability protocol.
- All associated Drug Master Files (DMFs) are acceptable or the pertinent information has been adequately provided in the application.
- The analytical methods used for testing (release, stability, and in-process) are well known and widely used by the pharmaceutical industry; revalidation by Agency laboratories will not be requested.

Overall Conclusion:

From a CMC perspective, the application is recommended for **Approval.**

Blair A. Fraser, Ph.D.
Director
DPA I/ONDQA

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Blair Fraser
10/2/2008 09:06:25 AM
CHEMIST

NDA 22-304

b(4)

[ ]

(Tapentadol hydrochloride)

Johnson & Johnson

John C. Hill, Ph.D.
ONDQA/DPMA-I and DAARP (HFD-170)

Chemistry Review #2

Table of Contents

Chemistry Review Data Sheet

1. NDA# 22-304

2. REVIEW # 2

3. REVIEW DATE: 29-SEP-2008

4. REVIEWER: John C. Hill, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
(N) Original NDA Filing	22-JAN-2008
(BL) Labeling update	13-MAR-2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
BC Response to CMC DR Letter	20-AUG-2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Ortho-McNeil-Janssen Pharmaceuticals, Inc.
Address:	Johnson & Johnson Pharmaceutical Research & Development, L.L.C. 1125 Trenton-Harbourton Road, P.O. Box 200 Titusville, NJ 08560-0200
	On behalf of
Representative:	Ortho-McNeil-Janssen Pharmaceuticals, Inc. 1125 Trenton-Harbourton Road, P.O. Box 200 Titusville, NJ 08560-0200 Kathleen F. Dusek, RPh, RAC Associate Director, Regulatory Affairs
Telephone:	(609) 730-2719

Fax: (609) 730-2986

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: [ ] b(4)
b) Non-Proprietary Name (USAN): Tapentadol hydrochloride
c) Code Name/# (ONDC only): R331333, CG5503,
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Antinociceptive agent

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 50, 75 and 100 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

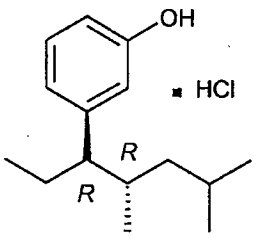
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X__Not a SPOTS product

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: $C_{14}H_{23}NO.HCl$
Molecular Weight: 257.80 g/mol; Free base: 221.34 g/mol
CAS: 175591-09-0



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS

b(4)

Chemistry Review Data Sheet

b(4)

21084	II	Janssen Pharmaceutica, N.V.	Tapentadol hydrochloride	1,4	Adequate	09-APR-2008	LOA: 23-JAN-2008 (From DMF Jacket)

*Review not required in accordance with review policy for container-closure systems for solid oral dosage forms.

[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
IND	61,345	TREATMENT OF MODERATE TO SEVERE PAIN

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	25-FEB-2008	S. FERGUSON(HFD-322)
Pharm/Tox	Acceptable	22-SEP-2008	Kathleen Young, Ph.D.
Biopharm	Acceptable	19-SEP-2008	Patrick Marroum, Ph.D.
LNC			
Methods Validation	Not Required		John C. Hill, Ph.D.

Chemistry Review Data Sheet

OPDRA			
EA	Adequate	07-JUL-2008	Raanan Bloom, Ph.D.
Microbiology			

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

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

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 22-304

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application has been reviewed and is recommended for APPROVAL from a CMC viewpoint.

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)

Drug Product

[ ](tapentadol HCl) tablets are immediate-release film-coated tablets available in 50, 75 and 100 mg strengths for oral administration. The label-strength is based on the molecular weight of the free acid tapenadol.[ ]tablets are provided as a [ ] b(4)

- 50 mg tablets are [ ] mm in diameter, yellow and debossed with "O-M" on one side and "50" on the other side, and are available in bottles of 100 (NDC[ ] and hospital unit dose blister packs of 10 (NDC[ ]
- 75 mg tablets are[ ]hm in diameter, yellow-orange and debossed with "O-M" on one side and "75" on the other side, and are available in bottles of 100 (NDC [ ] and hospital unit dose blister packs of 10 (NDC [ ]. b(4)
- 100 mg tablets are[ ]nm in diameter, orange and debossed with "O-M" on one side and "100" on the other side, and are available in bottles of 100 (NDC [ ] and hospital unit dose blister packs of 10 (NDC [ ] [ ].

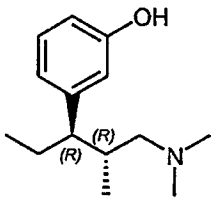
The inactive ingredients in[ ]tablets include microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, povidone, magnesium stearate, and Opadry® II, a proprietary film-coating mixture containing polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and aluminum lake coloring. [ ] b(4)
[ ]

The provided stability data support an 18-month expiry period.

Drug Substance

Tapentadol HCl is a centrally acting synthetic analgesic combining opioid and non-opioid activity in a single molecule. Although its exact mechanism is unknown, analgesic efficacy is thought to

be due to mu-opioid agonist activity and the inhibition of norepinephrine reuptake. The drug substance tapentadol hydrochloride has the chemical name 3-[(1*R*,2*R*)-3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol monohydrochloride and the following structure:



. HCl

The Molecular formula is $C_{14}H_{23}NO \cdot HCl$ and the molecular weight is 257.80 [redacted] for the free acid plus 36.46 for the HCl salt). The chemical structure of tapenadol HCl has been confirmed [redacted] b(4)

Data covering the manufacture, purification, characterization, regulatory specifications, container/closure and stability of the tapentadol hydrochloride drug substance are presented in DMF 21-084. This DMF has been reviewed in support of this NDA and found to be adequate.

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

[redacted] is indicated for the relief of moderate to severe acute pain. The dose is 50 mg, 75 mg, or 100 mg, taken orally, every 4 to 6 hours depending upon pain intensity. b(4)

C. Basis for Approvability or Not-Approval Recommendation

This NDA has been reviewed and is recommended for APPROVAL from a CMC viewpoint. This recommendation is based on the supporting developmental manufacturing and formulation data, supporting QbD and DoE data, chemical characterization, available stability data, and acceptable responses to the CMC Discipline Review Deficiency Comments.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

John C. Hill, Ph.D./Date:	Same date as review
Ali Al-Hakim, Ph.D., Branch Chief/	Same date as review

4 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

John C. Hill
9/30/2008 09:36:56 AM
CHEMIST

Ali Al-Hakim
9/30/2008 11:34:32 AM
CHEMIST

NDA 22-304

[ ] b(4)

(Tapentadol hydrochloride)

Johnson & Johnson

John C. Hill, Ph.D.
ONDQA/DPMA-I and DAARP (HFD-170)

Chemistry Review #1

Table of Contents

Chemistry Review Data Sheet

1. NDA# 22-304

2. REVIEW # 1

3. REVIEW DATE: 30-Jun-2008

4. REVIEWER: John C. Hill, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
(N) Original NDA Filing	22-JAN-2008
(BL) Labeling update	13-MAR-2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Ortho-McNeil-Janssen Pharmaceuticals, Inc.
Address:	Johnson & Johnson Pharmaceutical Research & Development, L.L.C. 1125 Trenton-Harbourton Road, P.O. Box 200 Titusville, NJ 08560-0200
	On behalf of
Representative:	Ortho-McNeil-Janssen Pharmaceuticals, Inc. 1125 Trenton-Harbourton Road, P.O. Box 200 Titusville, NJ 08560-0200 Kathleen F. Dusek, RPh, RAC Associate Director, Regulatory Affairs
Telephone:	(609) 730-2719

Fax: (609) 730-2986

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: [ ]
b) Non-Proprietary Name (USAN): Tapentadol hydrochloride
c) Code Name/# (ONDC only): R331333, CG5503,
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

b(4)

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

10. PHARMACOL. CATEGORY: Antinociceptive agent

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 50, 75 and 100 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
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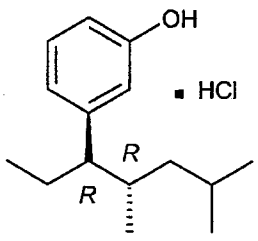
Chemical Name: 3-[(1*R*, 2*R*)-3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol monohydrochloride
Molecular formula: $C_{14}H_{23}NO.HCl$
Molecular Weight: 257.80 g/mol; Free base: 221.34 g/mol
CAS: 175591-09-0



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS

b(4)

b(4)

21084	II	Janssen Pharmaceutica, N.V.	Tapentadol hydrochloride	1,4	Adequate	09-APR-2008	LOA: 23-JAN-2008 (From DMF Jacket)

*Review not required in accordance with review policy for container-closure systems for solid oral dosage forms.

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3 – Reviewed previously and no revision since last review
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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
IND	61,345	TREATMENT OF MODERATE TO SEVERE PAIN

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	25-FEB-2008	S. FERGUSON(HFD-322)
Pharm/Tox	Pending		
Biopharm	Pending		
LNC			
Methods Validation	Not Required		

Chemistry Review Data Sheet

OPDRA			
EA	Adequate	07-JUL-2008	Raanan Bloom, Ph.D.
Microbiology			

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

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 22-304

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application has been reviewed and is approvable (AE) from a CMC viewpoint. Outstanding review issues are:

- Adequate responses to CMC deficiencies,
- Consultative Clin/pharm evaluation of animal tox studies,
- Consultative QbD/DoE evaluation by Manufacturing Sciences, and
- Consultative Biopharmaceutics evaluation of biowaver request.

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)

Drug Product

[ ]apentadol HCl) tablets are immediate-release film-coated tablets available in 50, 75 and 100 mg strengths for oral administration. The label-strength is based on the molecular weight of the free acid tapenadol.[ ]ablets are a[ ] b(4)

- 50 mg tablets are[ ]mm in diameter, yellow and debossed with "O-M" on one side and "50" on the other side, and are available in bottles of 100 (NDC[ ]) and hospital unit dose blister packs of 10 (NDC[ ] b(4)
- 75 mg tablets are[ ]m in diameter, yellow-orange and debossed with "O-M" on one side and "75" on the other side, and are available in bottles of 100 (NDC[ ] and hospital unit dose blister packs of 10 (NDC[ ].
- 100 mg tablets are[ ]m in diameter, orange and debossed with "O-M" on one side and "100" on the other side, and are available in bottles of 100 (NDC[ ] and hospital unit dose blister packs of 10 (NDC[ ] [ ]).

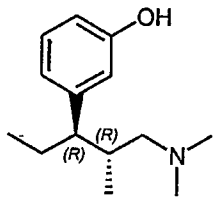
The inactive ingredients in[ ]tablets include microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, povidone, magnesium stearate, and Opadry® II, a proprietary film-coating mixture containing polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and aluminum lake coloring.[ ] b(4)

Chemistry Assessment

The provided stability data support an 18-month expiry period.

Drug Substance

Tapentadol HCl is a centrally acting synthetic analgesic combining opioid and non-opioid activity in a single molecule. Although its exact mechanism is unknown, analgesic efficacy is thought to be due to mu-opioid agonist activity and the inhibition of norepinephrine reuptake. The drug substance tapentadol hydrochloride has the chemical name 3-[(1*R*,2*R*)-3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol monohydrochloride and the following structure:



. HCl

The Molecular formula is $C_{14}H_{23}NO \cdot HCl$ and the molecular weight is 257.80 ( ) for the free acid plus 36.46 for the HCl salt). The chemical structure of tapenadol HCl has been confirmed

b(4)

Data covering the manufacture, purification, characterization, regulatory specifications, container/closure and stability of the tapentadol hydrochloride drug substance are presented in DMF 21-084. This DMF has been reviewed in support of this NDA and found to be adequate.

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

( ) is indicated for the relief of moderate to severe acute pain. The dose is 50 mg, 75 mg, or 100 mg, taken orally, every 4 to 6 hours depending upon pain intensity.

b(4)

C. Basis for Approvability or Not-Approval Recommendation

This NDA has been reviewed and found to be approvable. This recommendation is based on the supporting developmental manufacturing and formulation data, supporting QbD and DoE data, chemical characterization and stability data. Final evaluation of this application is pending, awaiting adequate responses to CMC deficiencies, consultative clin/pharm evaluation of animal tox studies, consultative QbD/DoE evaluation by manufacturing sciences, and consultative biopharmaceutics evaluation of the biowaver request.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

John C. Hill, Ph.D./Date: Same date as review
Ali Al-Hakim, Ph.D., Branch Chief/ Same date as review

C. CC Block

APPEARS THIS WAY
ON ORIGINAL

96 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

John C. Hill
7/21/2008 01:15:13 PM
CHEMIST

Ali Al-Hakim
7/21/2008 05:02:54 PM
CHEMIST

Initial Quality Assessment
Division of Pre-Marketing Assessment I, Branch II
Office of New Drug Quality Assessment
Division of Anesthesia, Analgesia and Rheumatology Products

OND Division:	Anesthesia, Analgesia and Rheumatology
NDA:	22-304
Applicant:	Johnson & Johnson
Stamp date:	January 23, 2008
PDUFA Date:	November 23, 2008
Trademark:	Not proposed
Established Name:	Tapentadol hydrochloride
Dosage Form:	Coated tablets 50, 75 and 100 mg
Route of Administration:	Oral
Indication:	Treatment of moderate to severe acute pain
Pharmaceutical Assessment Lead:	Danae D. Christodoulou, Ph.D.

	YES	NO
ONDQA Fileability:	√	___
Comments for 74-Day Letter:	√	___

APPEARS THIS WAY
ON ORIGINAL

Summary, Critical Issues and Comments

A. Summary

The application is filed as a 505(b)(1), non-priority NDA with 10-month review clock. Tapentadol hydrochloride is a New Molecular Entity (NME), but not a first in a class NME, since it is an analog of tramadol HCl (several approved products). The application is supported by IND 61,345 and a new Drug Master File, 21084, for tapentadol HCl.

Tapentadol HCl is a novel centrally acting antinociceptive agent, developed as an immediate-release (IR) tablet formulation for the relief of moderate to severe acute pain. Tapentadol is developed as a [ ] b(4)
[ ] Unlike tramadol, tapentadol has no clinically active metabolite(s). Tapentadol exhibits analgesic properties as a μ-opioid receptor (MOR) agonist and an inhibitor of norepinephrine re-uptake. Since both mechanisms are likely to contribute to the analgesic effects of tapentadol, this compound is different from the pure MOR agonists.

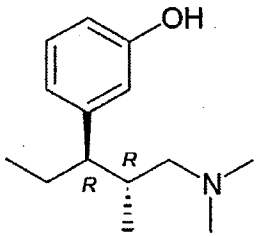
Tapentadol HCl tablets 50, 75 and 100 mg are film coated, immediate release tablets, administered twice daily. The tablets are packaged in [ ] bottles, counts 100 [ ] b(4)
[ ] and in blisters.

B. Review, Comments and Recommendations

Drug Substance

Molecular Structure, Chemical Name, Molecular Formula and Molecular Weight

3-[(1*R*, 2*R*)-3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol monohydrochloride
Molecular formula: $C_{14}H_{23}NO.HCl$
Molecular Weight: 257.80 g/mol; Free base: 221.34 g/mol
CAS: 175591-09-0



. HCl

The drug substance is referenced to the electronic Drug Master File (DMF) 21084, holder J&J. Originally tapentadol was developed at Grünenthal GmbH, Aachen Germany (GRT). The DMF was submitted on January 23, 2008 and, therefore, has not been reviewed previously. Note that there is no CMC information is included in the NDA. The following summaries of synthesis, impurity profile and batch analysis/stability have been copied from the DMF.

Tapentadol HCl is a ~~~~~ It is classified as a BCS Class I compound due to its high solubility, high permeability, and rapid dissolution according to the definitions in the FDA Guidance. Two dissociation constants (pKa values) were measured: pK_{a1} of 9.34 for the phenolic -OH moiety and pK_{a2} of 10.45 for the $-HN^{+}(CH_3)_2$ moiety.

Characterization:

[b(4)

15 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Fileability Template

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	√		
2	Is the section indexed and paginated adequately?	√		
3	On its face, is the section legible?	√		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	√		Contact names and telephone numbers not provided for the foreign sites
5	Is a statement provided that all facilities are ready for GMP inspection?	√		
6	Has an environmental assessment report or categorical exclusion been provided?	√		EA submitted
7	Does the section contain controls for the drug substance?	√		
8	Does the section contain controls for the drug product?	√		
9	Has stability data and analysis been provided to support the requested expiration date?	√		Stability data have been provided with no statistical analysis
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	N/A		**Supporting IND:** 61,345
11	Have draft container labels been provided?	√		
12	Has the draft package insert been provided?	√		
13	Has a section been provided on pharmaceutical development/ investigational formulations section?	√		
14	Is there a Methods Validation package?	√		
15	Is a separate microbiological section included?		√	
16	Have all consults been identified and initiated?	√ Pharm/Tox N/A Statistics N/A OCP/CDRH/CBER √ LNC √ DMETS/ODS N/A Microbiology		

Have all DMF References been identified? Yes (√) No ( )

DMF Number	Holder	Description	LoA Included	Status
21084 Type II	J&JPRD on behalf of Janssen Pharmaceutica. N.V.	Tapentadol HCl	Yes	pending

b(4)

b(4)

Danae D Christodoulou, Ph.D.
Pharmaceutical Assessment Lead

2/11/2008
Date

Ali Al-Hakim, Ph.D.
Branch II Chief

2/11/2008
Date

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/s/

Danae Christodoulou
2/12/2008 02:59:21 PM
CHEMIST
Initial Quality Assessment

Ali Al-Hakim
2/12/2008 03:57:51 PM
CHEMIST

August 26, 2008

From: Ying Wang
Branch of Manufacturing Science, Division of Pre-marketing Assessment III and Manufacturing Science, ONDQA

To: John Hill
Ali Al-Hakim
Branch II, Division of Pre-Marketing Assessment I, ONDQA

Cc: Rik Lostritto
Division III, ONDQA

Re: Consult for NDA 22-304

Per your request (attached in the end of review) I reviewed the two sections of NDA 22-304; formulation development and manufacturing process development. Here is the brief summary of my review (detail reviews are at the end of each section):

The overall formulation development methodology is sound.

b(4)

APPEARS THIS WAY
ON ORIGINAL

22 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

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/s/

Ying Wang
9/11/2008 09:46:27 AM
CHEMIST

Ali Al-Hakim
9/11/2008 10:09:04 AM
CHEMIST