CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-008

CHEMISTRY REVIEW(S)

NDA 22-008

(Review #2)

Requip® XL (ropinirole hydrochloride)
24-Hour Extended-Release Tablets
2mg, 3mg, 4mg, and 8mg

GlaxoSmithKline Corporation

Division of Neurology Drug Products

Donghao (Robert) Lu, Ph.D.

Division I of Pre-Marketing Assessment
Office of New Drug Quality Assessment

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Chemistry Review Data Sheet

1. NDA 22-008

2. REVIEW NUMBER: 2

3. REVIEW DATE: 19 November 2007

4. REVIEWER: Donghao (Robert) Lu, Ph.D.

5. PREVIOUS DOCUMENTS:

PREVIOUS DOCUMENTS	DOCUMENT DATE
NDA 22-008	9-FEB-07
NDA 22-008 (Amendment, Labeling)	9-MAR-07
NDA 22-008 (Amendment, CMC)	11-JUN-07
NDA 22-008 (Amendment, Labeling)	26-JUN-07

6. SUBMISSION(S) BEING REVIEWED:

SUBMISSION REVIEWED	DOCUMENT DATE
NDA 22-008 (Amendment, CMC Response)	19-NOV-07

7. NAME & ADDRESS OF APPLICANT:

NAME:	GlaxoSmithKline Corporation
ADDRESS:	One Franklin Plaza, P.O. Box 7929 Philadelphia, PA 19101
REPRESENTATIVE:	Elizabeth A. McConnell, Phm.D. Associate Director, Neurology US Regulatory Affairs
TELEPHONE:	919-483-6466

8. DRUG PRODUCT NAME/CODE/TYPE:

PROPRIETARY NAME	**Requip XL 24 Hour**
NON-PROPRIETARY NAME (USAN)	**Ropinirole Hydrochloride**
CODE NAME/ NUMBER (ONDC ONLY)	**SKF101468**
CHEMISTRY TYPE / SUBMISSION PRIORITY	**3S**

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

10. PHARMACOL. CATEGORY: Dopamine D_2/D_3-receptor agonist

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 2, 3, 4, 8 mg

13. ROUTE OF ADMINISTRATION: Oral

14. R_x/OTC DISPENSED: _x_ R_x ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

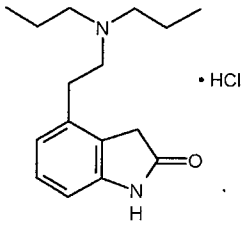
__x__Not a SPOTS product

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

Name (USAN): Ropinirole hydrochloride
Name (IUPAC): 4-[2-(Dipropylamino)ethyl]-2-indoline monohydrochloride
Name (CAS): 4-[2-(Dipropylamino)ethyl]-2-indoline monohydrochloride

(CAS) Registry Num: 91374-20-8

Structural Formula:



Mol. Formula: $C_{16}H_{24}N_2O$. HCl
Mol. Wt.: 296.84

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLET
	IV			4	N/A	
	III			4	N/A	
	III			4	N/A	
	III			4	N/A	
	III			4	N/A	
	III			4	N/A	
	III			4	N/A	
	III			4	N/A	

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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
NDA	20-658	ReQuip Tablets

18. STATUS:

CONSULTS & CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	29-MAR-07	S. Adams
Methods Validation	No validation request	14-SEPT-07	Donghao Lu, Ph.D.
ODS DMETS	[redacted]	11-OCT-07	Kimberly Pedersen
EA	Acceptable	14-SEPT-07	Donghao Lu, Ph.D.
Micro Consultation	N/A		

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The Chemistry Review for NDA 22-008

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The drug product Requip XL (ropinirole hydrochloride) 24-hour extended-release tablets, 2mg, 3mg, 4mg, and 8mg, is recommended as APPROVAL from a CMC perspective.

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 Substance and Drug Product

1. Drug Substance

The drug substance is ropinirole hydrochloride. The chemical name is 4-[2-(Dipropylamino)ethyl]-2-indoline monohydrochloride. It has a molecular formula of $C_{16}H_{24}N_2O \cdot HCl$ and its molecular weight is 296.84. All information regarding ropinirole hydrochloride drug substance is as approved for ReQuip® Tablets, NDA 20-658, and the cross reference was adequately provided. No additional information was submitted in this NDA for the drug substance section (3.2.S.).

2. Drug Product

The drug product is Requip® (ropinirole hydrochloride) XL 24-hour extended-release tablets, 2mg, 3mg, 4mg, and 8mg. It is intended for oral administration. Ropinirole controlled release (CR) tablets are developed for the treatment of Parkinson's Disease. The tablets contain 2, 3, 4 or 8 mg ropinirole (as ropinirole hydrochloride). All strengths are biconvex, capsule-shaped tablets (approximately 12.6 mm x 6.9 mm). Different debossings and film coat colors are used to aid identification of the different strengths. Control of drug release from Ropinirole CR tablets is achieved using the Geomatrix technology developed by SkyePharma. The tablet consists of a 3 layer core in which the central, active-containing, slow-release layer is sandwiched between ——— inactive barrier layers. The barrier layers serve to restrict the

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surface area available for release, thereby providing additional control over that provided by the active layer alone. Ropinirole CR Tablets are packed in ——— bottles, ———and child resistant closure ——— Inactive ingredients consist of carboxymethycellulose sodium, colloidal silicon dioxide, glyceryl behenate, hydrogenated castor oil, hypromellose, lactose monohydrate, magnesium stearate, maltodextrin, mannitol, povidone, and one or more of the following: carmine, FD&C Yellow No. 6 aluminum lake, FD&C Blue No. 2 aluminum lake, ferric oxides (black, red, yellow), polyethylene glycol 400, titanium dioxide. The manufacturing process of the products

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

Requip XL 24 hour CR drug products contain non-ergoline dopamine agonist and are indicated for the treatment of signs and symptoms of idiopathic Parkinson's disease. The recommended starting dose is 2 mg taken once daily for 1 —— followed by increases of 2 mg per day ———a maximum dose of 24 mg per day. The tablets are taken once daily, with or without meals. They must be swallowed whole and must not be chewed, crushed, or divided. The products should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). The products have an expiration period (shelf life) of 24 (for 2 and 3 mg strengths in—— bottle) and 36 months (for any other product configurations).

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C. Basis for Approvability or Not-Approval Recommendation

From a CMC perspective, GlaxoSmithKline has submitted sufficient and appropriate information to support the approval of the drug product. In our CMC review #1, there were several CMC issues which needed to be resolved before the final approval. GlaxoSmithKline has adequately addressed these CMC comments. Their responses and the CMC evaluations for these responses are described below.

III. Administrative

A. Reviewer's Signature

\s\ Donghao (Robert) Lu, Ph.D.

B. Endorsement Block

\s\ Ramesh Sood, Ph.D.

C. CC Block

3 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 2

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/s/

Donghao Lu
11/19/2007 01:50:45 PM
CHEMIST

Ramesh Sood
11/19/2007 01:52:17 PM
CHEMIST

CMC BRANCH CHIEF MEMORANDUM

To: NDA 22-008
From: Ramesh Sood, Branch Chief, ONDQA
Date: 7-Nov-2007
Subject: Approvable recommendation for NDA 22-008

Introduction: The Requip XL (ropinirole hydrochloride) extended release tablets, indicated for the treatment of signs and symptoms of idiopathic Parkinson's disease. The tablets will be available in 2 mg, 3 mg, 4 mg and 8 mg strengths. The labeled strength corresponds to the amount of ropinirole base.

Drug Substance: The drug substance used in the manufacture of Requip tablets is ropinirole hydrochloride. The chemical name is 4-[2-(dipropylamino)ethyl]-2-indoline monohydrochloride. It has a molecular formula of $C_{16}H_{24}N_2O$ .HCl and its molecular weight is 296.84. All CMC information for the drug substance has been cross-referenced to their approved ReQuip Tablets, NDA 20-658. No additional CMC information was provided in this NDA.

Drug Product: Requip tablets are designed to provide medication for up to 24 hours. All strengths are biconvex, capsule-shaped tablets with strengths differentiated from each other based on unique debossing and film coat colors. The control of drug release from the dosage form is achieved using the Geomatrix technology developed by SkyePharma. This technology has been used in a number of CDER approved products, including another GSK product, Paxil CR (paroxetine) tablets. Each tablet consists of a three layer core. The central, active-containing, slow-release layer is sandwiched between two ——— inactive barrier layers. The barrier layers restrict the surface area available for release of the active from the dosage form, hence, providing additional release control over the 24-hour period . The formulation of active-containing layer is qualitatively similar across strengths and contains ——— b(4)

The commercial drug product will be packaged in ——— bottles ———
——— The drug product is recommended to b(4)
be stored at 25°C. The product has been assigned a 24-month expiration date for 2 mg and 3 mg strengths packaged in——— bottles and 36 month for other strengths and packaging configurations.

All manufacturing sites have been found acceptable by Office of Compliance.

Recommended action: The CMC recommendation at the time of writing this memorandum is "Approvable". Some minor issues have been conveyed to the applicant and it is our expectation that the applicant will be able to provide a satisfactory response to these issues in this cycle. Subsequent to receiving response from the applicant, the reviewer will write a second review covering these issues with the final recommendation.

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/s/

Ramesh Sood
11/19/2007 09:26:02 AM
CHEMIST

NDA 22-008

Requip® XL (ropinirole hydrochloride)
24-Hour Extended-Release Tablets
2mg, 3mg, 4mg, and 8mg

GlaxoSmithKline Corporation

Division of Neurology Drug Products

Donghao (Robert) Lu, Ph.D.

Division I of Pre-Marketing Assessment
Office of New Drug Quality Assessment

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Chemistry Review Data Sheet

1. NDA 22-008

2. REVIEW NUMBER: 1

3. REVIEW DATE: 1 September 2007

4. REVIEWER: Donghao (Robert) Lu, Ph.D.

5. PREVIOUS DOCUMENTS:

PREVIOUS DOCUMENTS	DOCUMENT DATE

6. SUBMISSION(S) BEING REVIEWED:

SUBMISSION REVIEWED	DOCUMENT DATE
NDA 22-008	9-FEB-07
NDA 22-008 (Amendment, Labeling)	9-MAR-07
NDA 22-008 (Amendment, CMC)	11-JUN-07
NDA 22-008 (Amendment, Labeling)	26-JUN-07

7. NAME & ADDRESS OF APPLICANT:

NAME:	GlaxoSmithKline Corporation
ADDRESS:	One Franklin Plaza, P.O. Box 7929 Philadelphia, PA 19101
REPRESENTATIVE:	Elizabeth A. McConnell, Phm.D. Associate Director, Neurology US Regulatory Affairs
TELEPHONE:	919-483-6466

8. DRUG PRODUCT NAME/CODE/TYPE:

PROPRIETARY NAME	**Requip XL 24 Hour**
NON-PROPRIETARY NAME (USAN)	**Ropinirole Hydrochloride**
CODE NAME/ NUMBER (ONDC ONLY)	**SKF101468**
CHEMISTRY TYPE / SUBMISSION PRIORITY	**3S**

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

10. PHARMACOL. CATEGORY: Dopamine D_2/D_3-receptor agonist

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 2, 3, 4, 8 mg

13. ROUTE OF ADMINISTRATION: Oral

14. R_x/OTC DISPENSED: _x_ R_x ___OTC

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

_____SPOTS product – Form Completed

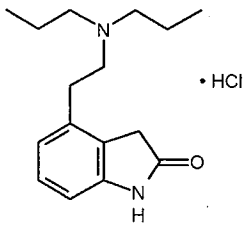
__x__Not a SPOTS product

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

Name (USAN): Ropinirole hydrochloride
Name (IUPAC): 4-[2-(Dipropylamino)ethyl]-2-indoline monohydrochloride
Name (CAS): 4-[2-(Dipropylamino)ethyl]-2-indoline monohydrochloride

(CAS) Registry Num: 91374-20-8

Structural Formula:



Mol. Formula: $C_{16}H_{24}N_2O$. HCl
Mol. Wt.: 296.84

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	COD E[1]	STATUS[2]	DATE REVIEW COMPLET
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	III			4	N/A	
	III			4	N/A	
	III			4	N/A	
	III			4	N/A	
	III			4	N/A	
	III			4	N/A	

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[1] Action codes for DMF Table:

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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
NDA	20-658	ReQuip Tablets

18. STATUS:

CONSULTS & CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	29-MAR-07	S. Adams
Methods Validation	No validation request	14-SEPT-07	Donghao Lu, Ph.D.
ODS DMETS	[redacted]	11-OCT-07	Kimberly Pedersen
EA	Acceptable	14-SEPT-07	Donghao Lu, Ph.D.
Micro Consultation	N/A		

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[redacted]

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The Chemistry Review for NDA 22-008

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The drug product Requip XL (ropinirole hydrochloride) 24-hour extended-release tablets, 2mg, 3mg, 4mg, and 8mg, is recommended as APPROVABLE from a CMC perspective, pending the acceptance of sponsor's responses for our CMC review comments (see the end of this document).

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 Substance and Drug Product

1. Drug Substance

The drug substance is ropinirole hydrochloride. The chemical name is 4-[2-(Dipropylamino)ethyl]-2-indoline monohydrochloride. It has a molecular formula of $C_{16}H_{24}N_2O \cdot HCl$ and its molecular weight is 296.84. All information regarding ropinirole hydrochloride drug substance is as approved for ReQuip® Tablets, NDA 20-658, and the cross reference was adequately provided. No additional information was submitted in this NDA for the drug substance section (3.2.S.).

2. Drug Product

The drug product is Requip® (ropinirole hydrochloride) XL 24-hour extended-release tablets, 2mg, 3mg, 4mg, and 8mg. It is intended for oral administration. Ropinirole controlled release (CR) tablets are developed for the treatment of Parkinson's Disease. The tablets contain 2, 3, 4 or 8 mg ropinirole (as ropinirole hydrochloride). All strengths are biconvex, capsule-shaped tablets (approximately 12.6 mm x 6.9 mm). Different debossings and film coat colors are used to aid identification of the different strengths. Control of drug release from Ropinirole CR tablets is achieved using the Geomatrix technology developed by SkyePharma. The tablet consists of a 3 layer core in which the central, active-containing, slow-release layer is sandwiched

between [redacted] inactive barrier layers. The barrier layers serve to restrict the surface area available for release, thereby providing additional control over that provided by the active layer alone. Ropinirole CR Tablets are packed in [redacted] bottles, [redacted] and child resistant closure [redacted] Inactive ingredients consist of carboxymethycellulose sodium, colloidal silicon dioxide, glyceryl behenate, hydrogenated castor oil, hypromellose, lactose monohydrate, magnesium stearate, maltodextrin, mannitol, povidone, and one or more of the following: carmine, FD&C Yellow No. 6 aluminum lake, FD&C Blue No. 2 aluminum lake, ferric oxides (black, red, yellow), polyethylene glycol 400, titanium dioxide. The manufacturing process of the products [redacted]

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

Requip XL 24 hour CR drug products contain non-ergoline dopamine agonist and are indicated for the treatment of signs and symptoms of idiopathic Parkinson's disease. The recommended starting dose is 2 mg taken once daily for 1 [redacted] followed by increases of 2 mg per day [redacted] . The tablets are taken once daily, with or without meals. They must be swallowed whole and must not be chewed, crushed, or divided. The products should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). The products have an expiration period (shelf life) of 24 (for 2 and 3 mg strengths in [redacted] bottle) and 36 months (for any other product configurations).

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C. Basis for Approvability or Not-Approval Recommendation

There are several CMC issues which need to be resolved before the final approval. The CMC issues are listed in the comments sent to the sponsor at the end of this document. These CMC comments have been sent to the sponsor.

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III. Administrative

A. Reviewer's Signature

\s\ Donghao (Robert) Lu, Ph.D.

B. Endorsement Block

\s\ Ramesh Sood, Ph.D.

C. CC Block

49 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 2

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/s/

Donghao Lu
11/7/2007 09:45:57 AM
CHEMIST

Ramesh Sood
11/8/2007 07:26:57 AM
CHEMIST