CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-008

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

NDA NUMBER: 22-008

NAME OF APPLICANT / NDA HOLDER: SmithKlineBeecham d/b/a GlaxoSmithKline

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME): Requip XL 24 Hour Extended Release Tablets

ACTIVE INGREDIENT(S): Ropinirole hydrochloride

STRENGTH(S): 2mg, 3mg, 4mg, and 8mg

DOSAGE FORM: Extended Release Tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number: 4,452,808

b. Issue Date of Patent: 1/5/1984

c. Expiration Date of Patent: 12/7/2007

d. Name of Patent Owner: SmithKline Beecham Corp.

Address *(of Patent Owner)*: Attn: Vice President, Corporate Intellectual Property
709 Swedeland Road
UW2220, P.O. Box 1539

City/State: King of Prussia, PA

ZIP Code: 19406-0939

FAX Number *(if available)*: (610) 270-5090

Telephone Number: (610) 270-5021

E-Mail Address *(if available)*: charles.m.kinzig@gsk.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address *(of agent or representative named in 1.e.)*:

City/State:

ZIP Code:

FAX Number *(if available)*:

Telephone Number:

E-Mail Address *(if available)*:

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

FORM FDA 3542a (7/03)

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?	☐ Yes	☐ No

Appears This Way
On Original

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
4.2 Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No	
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide information below)*

James C Kellerman

Date Signed: 11/9/06

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☒ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name James C. Kellerman	
Address GlaxoSmithKline 709 Swedeland Road UW 2220, P.O. Box 1539	City/State King of Prussia, PA
ZIP Code 19406-0939	Telephone Number (610) 270-5929
FAX Number *(if available)* (610) 270-5090	E-Mail Address *(if available)* james.c.kellerman@gsk.com

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

NDA NUMBER: 22-008

NAME OF APPLICANT / NDA HOLDER: SmithKlineBeecham d/b/a GlaxoSmithKline

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME): Requip XL 24 Hour Extended Release Tablets

ACTIVE INGREDIENT(S): Ropinirole hydrochloride

STRENGTH(S): 2mg, 3mg, 4mg, and 8mg

DOSAGE FORM: Extended Release Tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
4,824,860	4/25/1989	5/19/2008

d. Name of Patent Owner	Address *(of Patent Owner)*	
Smith Kline & French Laboratories Limited	Attn: Vice President, Corporate Intellectual Property 709 Swedeland Road UW2220, P.O. Box 1539	
	City/State: King of Prussia, PA	
	ZIP Code: 19406-0939	FAX Number *(if available)*: (610) 270-5090
	Telephone Number: (610) 270-5021	E-Mail Address *(if available)*: charles.m.kinzig@gsk.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

FORM FDA 3542a (7/03)

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?	☐ Yes	☐ No

Appears This Way
On Original

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 1	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* Treatment of signs and symptoms of idiopathic Parkinson's disease	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

8. Declaration Certification

8.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

8.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide information below)*

James C Kellerman

Date Signed: 11/9/06

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☒ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name: James C. Kellerman

Address	City/State
GlaxoSmithKline 709 Swedeland Road UW 2220, P.O. Box 1539	King of Prussia, PA
ZIP Code: 19406-0939	Telephone Number: (610) 270-5929
FAX Number *(if available)*: (610) 270-5090	E-Mail Address *(if available)*: james.c.kellerman@gsk.com

Appendix I: Section 4 Annex for FDA Form 3542a

4. Method of Use (continued)		
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:		
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment or supplement?		X Yes ☐ No
4.2 Patent Claim Number (as listed in the patent) 3	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement?	X Yes ☐ No
4.2a If the answer to 4.2 is "Yes," identify the use with specific reference to the proposed labeling for the drug product	*Use (Submit indication or method of use information as identified specifically in the approved labeling.)* Treatment of signs and symptoms of idiopathic Parkinson's disease	

Appears This Way
On Original

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
22-008

NAME OF APPLICANT / NDA HOLDER
SmithKlineBeecham
d/b/a GlaxoSmithKline

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Requip XL 24 Hour Extended Release Tablets

ACTIVE INGREDIENT(S)	STRENGTH(S)
Ropinirole hydrochloride	2mg, 3mg, 4mg, and 8mg

DOSAGE FORM
Extended Release Tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,422,123	6/6/1995	6/6/2012

d. Name of Patent Owner	Address *(of Patent Owner)*	
Jagotec AG	Eptingerstrasse 51	
	City/State: Muttenz, Switzerland	
	ZIP Code: CH-4132	FAX Number *(if available)*
	Telephone Number: (41) 61 467 5555	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
Charles M. Kinzig	Attn: Vice President, Corporate Intellectual Property 709 Swedeland Road UW2220, P.O. Box 1539	
	City/State: King of Prussia, PA	
	ZIP Code: 19406-0939	FAX Number *(if available)*: (610) 270-5090
	Telephone Number: (610) 270-5021	E-Mail Address *(if available)*: charles.m.kinzig@gsk.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

FORM FDA 3542a (7/03)

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?	☐ Yes	☐ No

Appears This Way
On Original

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
4.2 Patent Claim Number *(as listed in the patent)* — Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. — Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*		

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

8. Declaration Certification

8.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

8.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide information below)*	Date Signed
James C Kellerman	11/9/06

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/ holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name James C. Kellerman	
Address GlaxoSmithKline 709 Swedeland Road UW 2220, P.O. Box 1539	City/State King of Prussia, PA
ZIP Code 19406-0939	Telephone Number (610) 270-5929
FAX Number *(if available)* (610) 270-5090	E-Mail Address *(if available)* james.c.kellerman@gsk.com

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

NDA NUMBER
22-008

NAME OF APPLICANT / NDA HOLDER
SmithKlineBeecham
d/b/a GlaxoSmithKline

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Requip XL 24 Hour Extended Release Tablets

ACTIVE INGREDIENT(S)	STRENGTH(S)
Ropinirole hydrochloride	2mg, 3mg, 4mg, and 8mg

DOSAGE FORM
Extended Release Tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,626,874	5/6/1997	11/30/2014

d. Name of Patent Owner	Address *(of Patent Owner)*	
Ekita Investments N.V.	Eptingerstrasse 51	
	City/State: Muttenz, Switzerland	
	ZIP Code: CH-4132	FAX Number *(if available)*
	Telephone Number: (41) 61 467 5555	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
Charles M. Kinzig	Attn: Vice President, Corporate Intellectual Property 709 Swedeland Road UW2220, P.O. Box 1539	
	City/State: King of Prussia, PA	
	ZIP Code: 19406-0939	FAX Number *(if available)*: (610) 270-5090
	Telephone Number: (610) 270-5021	E-Mail Address *(if available)*: charles.m.kinzig@gsk.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

FORM FDA 3542a (7/03)

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?	☐ Yes	☐ No

Appears This Way
On Original

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
4.2 Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No	
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide information below)*

James C Kellerman

Date Signed: 11/9/06

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name James C. Kellerman	
Address GlaxoSmithKline 709 Swedeland Road UW 2220, P.O. Box 1539	**City/State** King of Prussia, PA
ZIP Code 19406-0939	**Telephone Number** (610) 270-5929
FAX Number *(if available)* (610) 270-5090	**E-Mail Address** *(if available)* james.c.kellerman@gsk.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

FORM FDA 3542a (7/03)

Page 4

EXCLUSIVITY SUMMARY

NDA # 22-008 SUPPL # HFD # 120

Trade Name Requip XL

Generic Name ropinirole extended-release tablets

Applicant Name GlaxoSmithKline

Approval Date, If Known June 12, 2008

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21-658 Requip Tablets

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☒

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study 169 "Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study of 6 months treatment with Ropinirole CR as adjunctive therapy in subjects with Parkinson's Disease Who are not Optimally Contolled on L-dopa"

Study 168 "Randomized, Double-Blind, 3-Period Crossover Study of Ropinirole CR and Ropinirole IR Monotherapy in Subjects with Early Phase Parkinson's Disease"

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study 169 "Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study of 6 months treatment with Ropinirole CR as adjunctive therapy in subjects with Parkinson's Disease Who are not Optimally Contolled on L-dopa"

Study 168 "Randomized, Double-Blind, 3-Period Crossover Study of Ropinirole CR and Ropinirole IR Monotherapy in Subjects with Early Phase Parkinson's Disease"

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 60,503	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND # 60,503	YES ☒	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in

interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Susan Daugherty
Title: RPM
Date: 6/12/08

Name of Office/Division Director signing form: Russell Katz, M.D.
Title: Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/

Russell Katz
6/30/2008 06:19:18 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 22-008 **Supplement Type (e.g. SE5):** N/A **Supplement Number:** _____

Stamp Date: 2-9-07 **PDUFA Goal Date:** 12-9-07

HFD-120 **Trade and generic names/dosage form: Requip (ropinirole) XL 24-Hour Tablets**

Applicant: GlaxoSmithKline **Therapeutic Class:** Anti-Parkinson Drugs

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

☒ **Yes. Please proceed to the next question.**

☐ **No. PREA does not apply. Skip to signature block.**

** SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.*

Indication(s) ***previously approved*** **(please complete this section for supplements only):** N/A

Each indication covered by current application under review must have pediatric studies: ***Completed, Deferred, and/or Waived.***

Number of indications for this application(s): 1

Indication #1: to treat signs and symptoms of idiopathic Parkinson's disease

Is this an orphan indication?

☐ **Yes. PREA does not apply. Skip to signature block.**

☒ **No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

☒ **Yes: Please proceed to Section A.**

☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**

☒ **Disease/condition does not exist in children**

☐ **Too few children with disease to study**

☐ **There are safety concerns**

☐ **Other:** _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Susan Daugherty
Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

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

/s/

Susan B. Daugherty
4/11/2007 11:11:36 AM

m. 1.3.3 Debarment Certification

NDA 22-008
Requip (ropinirole hydrochloride) XL, 24 Hour Extended Release Tablets
Treatment of signs and symptoms of idiopathic Parkinson's disease

DEBARMENT CERTIFICATION

GlaxoSmithKline hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

16 OCT 2006

Charles E. Mueller or Mertie V. Snead
Director, North America Clinical Compliance
Worldwide Regulatory Compliance

Date

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-008

SmithKline Beecham d/b/a/GlaxoSmithKline
Attention: Elizabeth McConnell, Pharm.D.
Associate Director, Regulatory Affairs, Neurology
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

Dear Dr. McConnell:

We acknowledge receipt on December 17, 2007, of your resubmission to your new drug application for Requip XL (ropinirole) Extended-Release Tablets.

We refer to your amendment dated January 30, 2008, containing information not previously submitted to your NDA. As discussed with you during the February 1, 2008, telephone call we now consider your NDA resubmission a class 2 response to our December 7, 2007 action letter. Therefore, the user fee goal date is June 17, 2008.

If you have any question, call me at (301) 796-0878.

Sincerely,

{See appended electronic signature page}

Susan Daugherty
Regulatory Health Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Susan B. Daugherty
2/1/2008 04:44:55 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-008

INFORMATION REQUEST LETTER

GlaxoSmithKline
Attention: Elizabeth A. McConnell, Pharm.D.
Project Director, Regulatory Affairs
P.O. Box 13398
Five Moore Drive
Research Triangle Park, NC 27709

Dear Dr. McConnell:

Please refer to your February 9, 2007, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Requip® (ropinirole hydrochloride) XL 24-hour™ Extended-Release Tablets 2 mg, 3 mg, 4mg, and 8 mg.

We also refer to your submissions dated March 9, 2007, June 11, 2007, and June 26, 2007.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA:

1. In P.3.5 Process Validation and/or Evaluation section, the in-process acceptance limits were listed in Table 8. However, the acceptance limit for the in-process control of damage inspection was not defined. Please define and add the acceptance limit.

2. In the post-approval stability commitment, you propose placing one commercial batch per tablet strength on stability. In accordance with ICH guideline ICH Q1A (R2), it is our expectation that the proposed shelf life should be confirmed by stability studies on at least 3 production batches per strength placed under long-term and accelerated storage conditions. We recognize that one production scale batch, each of 2, 4 and 8 mg strength, has been placed on stability. However, the post-approval stability commitment should be revised to include a total of at least three production batches per strength (you may continue to bracket out the 3 mg strength) to support the proposed shelf life. Revise your post-approval stability commitment accordingly.

NDA 22-008
Chemistry, Manufacturing and Controls
Information Request Letter

If you have any questions, call Scott N. Goldie, Ph.D., Regulatory Health Project Manager for Quality, at (301) 796-2055.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

Ramesh Sood
11/7/2007 01:45:47 PM

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: October 29, 2007

TO: Susan Daugherty, Regulatory Project Manager
Leonard Kapcala, M.D., Clinical Reviewer
Division of Neurology Products, HFD-120

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

FROM: Sherbet Samuels, R.N., M.P.H.

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-008

APPLICANT: GlaxoSmithKline

DRUG: Requip XL 24 Hour (ropinirole) Tablets

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of the signs and symptoms of idiopathic Parkinson's disease

CONSULTATION REQUEST DATE: July 13, 2007

DIVISION ACTION GOAL DATE: November 1, 2007

PDUFA DATE: December 9, 2007

I. BACKGROUND:

Requip is approved for the treatment of signs and symptoms of idiopathic Parkinson's disease. The sponsor has submitted a new drug application (NDA # 22-008) for marketing approval of an extended release formulation of Requip for the treatment of signs and symptoms of idiopathic Parkinson's disease. Jan Ilkowski, M.D., Andrzej Szczudlik, Prof., and Grzegorz Maciej Opala, M.D., Ph.D., Prof. were inspected for protocol SK&F 101468/169 entitled "A Phase III, Randomized, Double-blind, Placebo-controlled, Parallel Group Study of Six Months Treatment with Ropinirole CR as Adjunctive Therapy in Patients with Parkinson's Disease who are not Optimally Controlled on L-dopa". These foreign sites were selected for inspection because there are insufficient domestic data. In addition, domestic and foreign data

show conflicting results pertinent to decision-making (U.S. sites as a whole tend to support the sponsor's claim but many foreign sites (except for Poland) do not tend to support the sponsor's claim). The goals of the inspection were to assess adherence to FDA regulatory requirements: specifically, investigator oversight, protocol compliance, validity of primary efficacy endpoint data, and protection of subjects' rights, safety, and welfare.

Summary Report of Foreign Inspections

II. RESULTS (by protocol/site):

Name of CI and site #	City	Country	Protocol	Inspection Date	EIR Received Date	Final Classification
Jan Ilkowski, M.D. Site 103	Poznan	Poland	SK&F 101468/169	October 22-24, 2007	EIR Pending	Pending
Andrzej Szczudlik, Prof.. Site 024	Krakow	Poland	SK&F 101468/169	October 15-18, 2007	EIR Pending	Pending
Grzegorz Maciej Opala, M.D., Ph.D., Prof. Site 022	Katowice	Poland	SK&F 101468/169	October 8-11, 2007	EIR Pending	Pending

Key to Classifications
NAI = No deviation from regulations.
VAI-No Response Requested= Deviations(s) from regulations. See specific comments below for data acceptability
VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability
OAI = Significant deviations from regulations. See specific comments below for data acceptability

Protocol # SK&F 101468/169

1. Jan Ilkowski, M.D. [Site 103]
   Department of Neurology
   City Hospital Poznan
   3 Szwajcarska street
   61-285 Poznan
   Poland

a. What was inspected: Dr. Ilkowski enrolled 15 subjects. The inspection encompassed an audit of all subjects' records. Primary endpoint efficacy data were verified for all subjects.

b. Limitations of inspection: Some source documents (i.e. progress notes) were in the foreign language. There were no other limitations.

c. General observations/commentary: The inspection found protocol violations. Specifically, treatment dosing did not always follow protocol requirements. Subjects 6065, 6079 and 5960 were on a combination of Madopar and Madopar HBS at enrollment. For each of these subjects the Madopar was decreased at weeks 3, 4, 6, 8 and 10 as opposed to the Madopar HBS.

Note: Observations noted above are based on the Form FDA 483, Inspectional Observations and communications from the FDA Investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

d. Data acceptability/reliability: Data appear acceptable.

2. Andrzej Szczudlik, Prof. [Site 024]
Centrum Neurologii Klinicznej
Ul. Dwernickiego 8
31-530 Krakow
Poland

a. What was inspected: Prof. Szczudlik enrolled 20 subjects. The inspection encompassed an audit of all subjects' records. Primary endpoint efficacy data were verified for all subjects.

b. Limitations of inspection: Some source documents (i.e. progress notes) were in the foreign language. There were no other limitations.

c. General observations/commentary: The inspection found protocol violations. Specifically,

ECG were not performed at the following visits:
Subject 5953 – follow-up visit 8 Sept 04
Subject 5049 – follow-up visit 25 Aug 04
Subject 5951 – Week 12 visit 9 Jun 04, follow-up visit 8 Sep 04
Subject 5954 – Week 12 visit 23 Jun 04, follow-up visit 22 Sep 04

Subjects 5961 and 5956 were on a combination of Madopar and Madopar HBS at enrollment. For subject 5961 Madopar was decreased at weeks 3, 4 and 6 as opposed to the Madopar HBS. For subject 5956 Madopar was decreased at weeks 3, 4, 6, 8 and 10 as opposed to the Madopar HBS.

Note: Observations noted above are based on the Form FDA 483, Inspectional Observations and communications from the FDA Investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

d. Data acceptability: Data appear acceptable.

3. Grzegorz Maciej Opala, M.D., Ph.D., Prof. [Site 022]
Department of Neurology, Ageing, Degenerative & Cerebrovascular Disease
Ul. Medykow 14
40-588 Katowice
Poland

a. What was inspected: Dr. Opala enrolled 20 subjects. The inspection encompassed an audit of all subjects' records. Primary endpoint efficacy data were verified for all subjects.

b. Limitations of inspection: Some source documents (i.e. progress notes) were in the foreign language. There were no other limitations.

c. General observations/commentary: The inspection found a protocol violation. Specifically, treatment and dosing did not always follow protocol requirements. For subject 5968, the l-dopa level was increased at week 6 due to increased symptoms of Parkinson's in violation of the protocol.

Note: The observation noted above is based on the Form FDA 483, Inspectional Observations and communications from the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

d. Data acceptability: Data appear acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

As mentioned above, the inspection of Jan Ilkowski, M.D., Andrzej Szczudlik, Prof., and Grzegorz Maciej Opala, M.D., Ph.D., Prof. found protocol violations. The data from these sites appear acceptable in support of the respective indication.

As previously mentioned, observations noted above are based on the Form FDA 483, Inspectional Observations and communications from the FDA Investigator. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIR.

{See appended electronic signature page}

Sherbet Samuels, R.N., M.P.H.

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

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

/s/

Sherbert Samuels
10/30/2007 07:12:53 AM
CSO

Constance Lewin
10/31/2007 10:06:29 AM
MEDICAL OFFICER

DSI CONSULT: Request for Clinical Inspections

Date: July 13, 2007

To: Constance Lewin, M.D., M.P.H., Branch Chief, GCP1, HFD-46
Leslie Ball, M.D., Branch Chief, GCP2, HFD-47

cc: Gary Della'Zanna, D.O, Director, Division of Scientific Investigations, HFD-45

From: Susan Daugherty, Regulatory Project Manager, HFD-120
Division of Neurology Products (DNP)

Subject: **Request for Clinical Site Inspections**
NDA 22-008
GlaxoSmithKline
Requip XL 24 Hour (ropinirole) Tablets

Protocol/Site Identification:

The sponsor's claim for ER-ropinirole (REQUIP XL 24-HOUR) is that it is indicated for the treatment of the signs and symptoms of idiopathic Parkinson's disease.

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority.

The DNP recommends inspections at the first 2 sites (#s 103-Poznan and 24-Krakow)) and if possible, also at the third site (# 22) in Katowice that is close to the site in Krakow.

Investigator	Sub-investigator(s)	Hospital/ Institution and Address	IEC/IRB Committee Chair and Name of Committee	Investigator/ Site no.	Placebo (N)*	Ropinirole CR (N)*
Jan Ilkowski, MD		Department of Neurology City Hospital Poznan 3 Szwajcarska street 61-285 Poznan POLAND	Komisja Bioetyczna przy Okregowej Radzie Lekarskiej Wielkopolskiej (Bioethics Committee at Regional Medical Council of Wielkopolska Medical Chamber) Chairman: Maria de Mezer-Dambek, PhD	103	8	7

b(4)

__X__ Other: Results from several sites in Poland enrolling relatively large numbers of patients support a therapeutic benefit in contrast to results in other foreign countries that tend not to support that claim.

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by 11/1/07. We intend to issue an action letter on this application by December 9, 2007. The PDUFA due date for this application is 12/9/07.

Should you require any additional information, please contact Susan Daugherty @ (301) 796-0878.

Concurrence:

John Feeney, Acting Deputy Director
Leonard Kapcala, Medical Reviewer
Russell Katz, Division Director (for foreign inspection requests only)

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

/s/

Susan B. Daugherty
7/18/2007 10:39:57 AM

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-008 Supplement # Efficacy Supplement Type SE-

Proprietary Name: Requip XL 24 Hour Extended-Release Tablets
Established Name: ropinirole
Strengths: 2 mg, 3 mg, 4 mg, and 8 mg
Applicant: SmithKline Beecham Corporation d/b/a GlaxoSmithKline

Date of Application: 02/09/07
Date of Receipt: 02/09/07
Date clock started after UN: N/A
Date of Filing Meeting: 03/27/07
Filing Date: 4/10/07
Action Goal Date (optional): User Fee Goal Date: 12/09/07

Indication requested: Treatment of signs and symptoms of idiopathic Parkinson's disease

Type of Original NDA: (b)(1) ☒ (b)(2) ☐
AND (if applicable)
Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:
(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S ☒ P ☐
Resubmission after withdrawal? ☒ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 3
Other (orphan, OTC, etc.) N/A

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES ☒ NO ☐

If yes, explain:

NDA 20-658 Requip Tablets -indication exclusivity - treatment of moderate to severe Restless Legs Syndrome until May 4, 2008

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?
  YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐
  If no, explain:

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES ☐

2. This application is an eNDA or combined paper + eNDA YES ☒
   This application is: All electronic ☒ Combined paper + eNDA ☐
   This application is in: NDA format ☐ CTD format ☒
   Combined NDA and CTD formats ☐
   Does the eNDA, follow the guidance?
   (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES ☒ NO ☐

   Additional comments: Supporting data are contained in NDA 21-035/S-050 and NDA 21-505/S-009 and are located in the EDR.

3. This application is an eCTD NDA. YES ☐ NO ☒
   If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

   Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Exclusivity requested? YES, ☒ NO ☐
  3 Years

  NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
  YES ☒ NO ☐

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES ☒ NO ☐

- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO ☒

  If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
  (Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section) YES ☒ NO ☐
- PDUFA and Action Goal dates correct in tracking system? YES ☒ NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

b(4)

- List referenced IND numbers: [redacted] 60,503; [redacted].

- Are the trade, established/proper, and applicant names correct in COMIS? YES ☒ NO ☐
  If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) October 13, 2007 YES ☒
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) _____ NO ☒
  If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO ☒

If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES ☒ NO ☐
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES ☒ NO ☐

  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES ☒ NO ☐

  - If Rx, trade name (and all labeling) consulted to OSE/DMETS? ☒ NO ☐

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  N/A ☒ YES ☐ NO ☐

- Risk Management Plan consulted to OSE/IO? N/A ☒ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA ☒ YES ☐ NO ☐

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES ☐ NO ☐

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A
  YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to EA officer, OPS? YES ☐ NO ☐

- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☒ NO ☐

- If a parenteral product, consulted to Microbiology Team? YES ☐ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: 3/27/07

NDA #: 22-008

DRUG NAMES: Requip (ropinirole) XL 24-Hour Extended-Release Tablets

APPLICANT: SmithKline Beecham d/b/a GlaxoSmithKline

BACKGROUND: This application contains labeling that complies with the Physician's Labeling Rule.

ATTENDEES: Russell Katz, M.D., Director; John Feeney III, M.D., Medical Team Leader; Leonard Kapcala, M.D., Medical Reviewer; Dave Podskalny, M.D., Medical Reviewer; Lois Freed Ph.D., Supervisory Pharmacologist; Martha Heimann, Ph.D., Pharmaceutical Assessment Lead; Dunghao Lu, Ph.D., Chemistry Reviewer; Ramana Uppoor, Ph.D. Clinical Pharmacology Team Leader; Ta-Chen Wu, Ph.D, Clinical Pharmacology Reviewer; Susan Daugherty, Regulatory Project Manager

ASSIGNED REVIEWERS (including those not present at filing meeting):

Discipline/Organization	**Reviewer**
Medical:	Leonard Kapcala, M.D.
Statistical:	Sharon Yan, Ph.D.
Pharmacology:	TBD
Chemistry:	Dunghao Lu, Ph.D.
Environmental Assessment (if needed):	N/A.
Biopharmaceutical:	Ta-Chen Wu, Ph.D.
Microbiology, sterility:	N/A
DSI:	
Regulatory Project Management:	Susan Daugherty
Other Consults:	DMETS

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site audit(s) needed? YES ☒ NO ☐
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
  N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

STATISTICS	N/A	☐	FILE	☒	REFUSE TO FILE	☐	
BIOPHARMACEUTICS			FILE	☒	REFUSE TO FILE	☐	
• Biopharm. study site audits(s) needed?					YES ☐	NO	☒
PHARMACOLOGY/TOX	N/A	☐	FILE	☒	REFUSE TO FILE	☐	
• GLP audit needed?					YES ☐	NO	☒
CHEMISTRY			FILE	☒	REFUSE TO FILE	☐	
• Establishment(s) ready for inspection?					YES ☐	NO	☐
• Sterile product?					YES ☐	NO	☒
If yes, was microbiology consulted for validation of sterilization?							
				N/A ☒	YES ☐	NO	☐

ELECTRONIC SUBMISSION:
Any comments: Submitted via Electronic Gateway.

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☒ No filing issues have been identified.
- ☐ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. ☒ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4. ☒ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5. ☒ Convey document filing issues/no filing issues to applicant by Day 74.

Susan Daugherty
Regulatory Project Manager

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

/s/

Susan B. Daugherty
4/11/2007 10:54:41 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-008

SmithKline Beecham d/b/a/GlaxoSmithKline
Attention: Elizabeth McConnell, Pharm.D.
Associate Director, Regulatory Affairs, Neurology
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

Dear Dr. McConnell:

Please refer to your February 9, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Requip® (ropinirole) XL 24-hour™ Extended-Release Tablets 2 mg, 3 mg, 4mg, and 8 mg.

We also refer to your submissions dated March 9 and 22, 2007.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on April 10, 2007 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issue:

> With respect to product labeling, we recommend that the established name for the product be consistent with the expression of potency. Please revise the established name to "ropinirole extended-release tablets." We also recommend that you apply for designation of ropinirole (base) as the United Stated Adopted Name (USAN).

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following:

1. A package insert that combines the Requip® Tablet and Requip® XL 24-Hour™ package inserts.
2. Please provide all the PK and in-vitro dissolution data used for establishing IVIVC in SAS .XPT files.

Please respond only to the above request for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Susan Daugherty, Regulatory Project Manager, at (301) 796-0878.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Russell Katz
4/24/2007 04:35:42 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-008

NDA ACKNOWLEDGMENT

SmithKline Beecham d/b/a/GlaxoSmithKline
Attention: Elizabeth McConnell, Pharm.D.
Associate Director, Regulatory Affairs, Neurology
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

Dear Dr. McConnell:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Requip® (ropinirole) XL 24-hour Extended-Release Tablets 2 mg, 3 mg, 4mg, and 8 mg

Review Priority Classification: Standard

Date of Application: February 9, 2007

Date of Receipt: February 9, 2007

Our Reference Number: NDA 22-008

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 10, 2007 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be December 9, 2007.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are waiving the requirement for pediatric studies for this application.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neurology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call Susan Daugherty, Regulatory Project Manager, at (301) 796-0878.

Sincerely,

{See appended electronic signature page}

Susan Daugherty
Regulatory Health Project Manager
Division of Neurology Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

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

/s/

Susan B. Daugherty
3/14/2007 11:05:21 AM

From: Wheelous, Teresa A
Sent: Tuesday, May 02, 2006 3:31 PM
To: 'betty.a.mcconnell@gsk.com'
Subject: NDA 22008 Ropinirole

Elizabeth,

the following is another clinical comment regarding NDA 22-008:

- For studies 168 and 169, please provide separate analyses of clinical laboratory results (for each analyte) according to dose (up to 8 mg/d, > 8 -16 mg/d, > 16-24 mg/d, and any dose). The DNP believes that these data analyses will be more sensitive for detecting and characterizing treatment effects on laboratory analytes. Please also present pooled laboratory data analyses for studies 168 and 169 (and 228 if unblinded data are available) according to treatment group and dose (described above) as requested for the separate analyses of studies 168 and 169.

Regards,

CDR Teresa Wheelous, R. Ph.
Sr. Regulatory Management Officer
FDA
Division of Neurology
10903 New Hampshire Avenue, Bldg. #22
Silver Spring, MD 20993-0002
(telephone) 301-796-1161
(fax) 301-796-9842
New email address: teresa.wheelous@fda.hhs.gov

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

/s/

Teresa Wheelous
5/12/2006 03:11:18 PM
CSO

The following requests were compiled by the DNP. Most of these requests were presented at the meeting between the DNP and sponsor on 3/13/06. Some requests were discussed in more depth than others. Because of time constraints, there was not sufficient time to discuss all these requests. Such requests are noted under the category Not Specifically Discussed. This document will also serve as minutes of the meeting.

General Comments/Recommendations

- Provide an Integrated Summary of Safety (ISS) that should comprehensively integrate safety findings/analyses (for all treatment-emergent adverse events-TEAEs including deaths, serious adverse events-SAEs, discontinuations for TEAEs, TEAEs of special interest, vital sign analyses, laboratory analyses, ECG analyses) **across studies** and that should not merely summarize findings in individual studies or refer the reader to these individual studies.

  In particular, we refer you to the guidance, Guidance for Industry M4: The CTD — Efficacy Questions and Answers:

  "The ISS/ISE are critical components of the safety and effectiveness submission and are expected to be submitted in the application in accordance with the regulation. FDA's guidance *Format and Content of Clinical and Statistical Sections of Application* gives advice on how to construct these summaries. Note that, despite the name, these are integrated analyses of all relevant data, not summaries.

  The Clinical Safety sections of the CTD follow approximately the outline of the sections of the ISS/ISE, although they are somewhat modified by experience with ICH E-3 (*Structure and Content of Clinical Study Reports*). The CTD Clinical Overview and Summary in Module 2 will not usually contain the level of detail expected for an ISS. It may contain the level of detail needed for an ISE, but this would need to be determined on a case-by-case basis."

  We do not think that you need to provide an ISE but think that the Clinical Summary of Efficacy will suffice because the efficacy data across studies does not provide significant information beyond that provided from each of the individual study reports.

  We recommend that you review the following guidances for assistance in planning your NDA submission in general but in particular for planning the details about the format and content of your ISS:

- Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review
- Guidance for Industry M4: The CTD — Efficacy Questions and Answers
- Format and Content of Clinical and Statistical Sections of Application
- Format and Content of the Summary for New Drug and Antibiotic Applications
- Formatting, Assembling and Submitting New Drug and Antibiotic Applications
- Regulatory Submissions in Electronic Format; General Considerations

  You can contact the division for advice if unusual questions arise as to the content and format of your submission and the answers are not contained in any of these guidances.

We request that you construct the ISS in accordance with the ISS section (including all sections/subsections) of the Clinical Reviewer's Template and as recommended in the guidance, Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review (2/05) which reviews these specific sections. Please also provide tables using the formats shown in the example tables/listings at the end of this guidance.

- Provide tabular information about exposure to all Parkinson's Disease patients according to dose AND duration :
  - Focus showing the number of patients with any exposure to ER ropinirole and exposure $\geq$ 6 months and $\geq$ 12 months according to 3 dose ranges (up to 8 mg/d, > 8 – 16 mg/d, > 16 – 24 mg/d) and any dose
  - Dose exposure can be based upon modal dose (i.e. dose most commonly used during that period)
  - Patients in each dose range category should be exclusive to that range and not contained also in another range
  - The DNP would like to confirm that data in table 4.7 (m 5.3.7.5) can show exposure of the same patient in different dose duration categories and that these data are not exclusive to a certain dose duration treatment.

- Some analyses from controlled studies should be based upon pooling results of patients across studies. Although all safety analyses from studies 168 and 169 should be conducted separately according to each study, we are also interested in pooling results of the controlled portions of these studies for laboratory results and ECGs. Thus, there would be separate laboratory results and separate ECG results for each study (in addition to all the separate analyses for each study), but there would also be a pooled analysis of laboratory results based upon pooling patients from studies.

  In addition, you should also pool the open-label extension safety experience from the various studies for TEAEs, deaths, SAEs, and study discontinuations for TEAEs, laboratory results, VS results, and ECG results. This pooling should be based upon an operational definition of whether the patient is categorized as "early" Parkinson's Disease or "advanced" Parkinson's Disease. Although some patients might progress from early to advanced disease while participating in the extension study, it was agreed that you would provide an operational definition for determining in which pool (e.g. early or advanced) to place the patient.

- Please provide assurance or justification why your planned schedule for safety data collection at the "end" of the study may not have resulted in deficient safety data collection. Ordinarily, the "last", follow-up visit in a study occurs at some time 7-30 days after the last day of study treatment administration. According to information provided from studies 168 and 169, the safety follow-up visit was scheduled "4 to 14 days after the last dose of study medication" but a considerable percentage of patients may have continued study treatment (in the down titration phase) after this "last" safety, follow-up visit. In such instances, not only might there not be data collected while the patient continued study treatment but there might not be data collected in the period immediately after complete discontinuation of study treatment. You noted that many of these patients may have entered an open label, extension phase and had data safety data collection. You should provide clarification to allay the DNP concerns expressed here.

- Provide individual subject data listings for all studies. These listings should be cross-referenced when used as a data source for a summary table along with a hyperlink to any and all source data specified in a table or figure.

Analyses of Adverse Events

- For studies 168 and 169, provide separate analyses of treatment-emergent adverse events (TEAEs) including deaths, serious adverse events (SAEs), and discontinuations for TEAEs. Please analyze these data according to treatment and ropinirole dose (up to 8 mg/d, > 8 -16 mg/d, > 16 -24 mg/d, and any dose) for : 1) titration phase; 2) maintenance phase; and 3) onset during titration and persistence into maintenance phase.

  Guideline for characterizing the titration period: If there was no protocol specified detailed instruction for how to conduct the up-titration until a maximal "dose" was achieved or a constant titration phase was not applicable to all patients in a study, define the end of the titration phase for each patient according to an operational definition. You could characterize the "end" of the titration period by determining when each patient had remained on a stable "dose" of study treatment for a period of $\geq$ 3 weeks during the beginning of the study in the up-titration period. When that period has been determined, define the end of the titration period as 7 days after the patient had been on that "stable dose" of study treatment. For example if a patient gradually increased the dose of ER ropinirole up to a "maximal" dose of 8 mg (starting this dose at the beginning of week 4) during the up-titration phase and then remained on that dose for $\geq$ 3 weeks, the end of this patient's titration phase would be defined as the end of week 4 (i.e. 7 days/1 week after initiating treatment with the "maximal" dose). If you choose a different operational definition for characterizing/defining the end of the titration phase for each patient, please submit this operational definition to the clinical reviewer for acceptability prior to conducting analyses based upon your operational definition.

  Guideline for characterizing a TEAE as "persistent": You will also need to define this last category (e.g. when a TEAE with onset in the titration phase is considered "persistent" in the maintenance phase. For example you might consider such an event as "persistent: if an event starting in the titration period persists > 7 days into the maintenance period).

  In all of these analyses, also show the total number of specific events and the total number of patients experiencing each event in addition to the incidence data.

- For study 168, present TEAEs (and also for SAEs, and discontinuations for TEAEs) by formulation (e.g. not by combined pattern of 3 consecutive maintenance periods including one cross-over treatment from IR ropinirole to ER ropinirole or vice versa in the maintenance period) in different periods (i.e. T, M1,M2,M3). Patients with 3 consecutive maintenance periods will have 2 consecutive maintenance periods with the same formulation and also 1 maintenance period with the alternative formulation. In the requested analyses, all results from any maintenance period (e.g. M1 or M2 or M3) would be combined and shown according to the same formulation (i.e. IR or ER) regardless of how many maintenance periods there were for that formulation or what formulation was used in the titration phase. Thus, these analyses when completed would show the frequency of TEAEs for the titration period for IR vs ER and then the frequency of TEAEs for the maintenance period for IR vs ER.

- A question was raised: How can you assure that ALL TEAEs were captured comprehensively if the protocol told investigators not to count an AE as a TEAE if it was related to the disease or disease progression or to a medical or surgical procedure? For example, if a patient had a coronary catheterization and/or emergency coronary bypass surgery because the patient presented with chest pain resulting from hypotension, would the event have been captured as a SAE for chest pain that eventually resulted in an admission for a procedure? It is also noted that it can be difficult at times to distinguish some adverse events from being an adverse drug reaction vs a manifestation of the disease or disease progression.

- Present separate summary tables of age and gender incidence of preferred term TEAEs (only when $\geq$ 2 % for ER ropinirole and also > than placebo % from whole trial and any dose). Each table should show the incidence of TEAEs (and # patients in each column) according to treatment during titration period or maintenance period, and also dose (up to 8 mg/d, > 8 – 16 mg/d, > 16 – 24 mg/d and any dose) during titration and maintenance phases. There should be a separate tables for comparing results in the titration phase and in the maintenance phase. Columns of data for males vs females and for 18-64 vs $\geq$ 65 years old should be shown along side each other in the same table. Each table may need to be shown in continuous fashion on more than one page because of a large number of adverse events being compared.

- Present all 3 categories of narratives (SAEs, discontinuations for TEAEs, TEAEs of special interest) that DNP desires in a single location in the ISS. Within each of the 3 categories, present narratives according to study. If the narratives are constructed chronologically (as we believe they are) and could contain many paragraphs describing several events surrounding many different SAEs, please hyperlink the term(s) describing the TEAE in the comprehensive table of all narratives to the specific section of the narrative dealing with that specific TEAE. This specific request is made because some chronological narratives can be quite long and complicated and include many paragraphs describing many TEAEs prompting a narrative over 2 or more pages. Hyperlink all references (within a study report) to a specific patient experiencing a TEAE requiring a narrative to the specific narrative located in the ISS section. Please also provide a simple TOC for all subjects with narratives at the beginning of the section containing narratives and specify the page location of each subject's narrative.

  All narratives should contain known, important information not only about the study treatment (especially dose) prior to, during the course and resolution of the TEAE, but also similar information about any other treatments that may have impacted on the development, course, or resolution of the TEAE.

  Please provide narratives in a single location in the ISS also for normal volunteers (who were not patients) experiencing an SAE, TEAE causing study discontinuation, or TEAE of special interest (for subjects in whom a narrative is required for a non-serious TEAE of special interest; see guidelines for when a narrative is required and please follow the recommendations for narratives shown above for Parkinson's Disease patients).

  Please provide a comprehensive table of all patients similar to the one shown in Appendix 1 of the Clinical Summary of Safety but also specify age, gender, and study treatment dose for each patient and provide a hyperlink of the TEAE in the table to the specific section of the narrative that describes that TEAE. If a patient has more than one TEAE requiring a narrative, information on that patient can be presented in a single row in the table but each TEAE requiring a narrative should be separately hyperlinked to the specific section of the narrative describing that TEAE. Provide a

separate, similar comprehensive table (including hyperlinks) of narratives for non-patient subjects as is requested for patients.

- The DNP requests similar safety analyses (as are being requested studies 168 and 169) for study 228 when available. The question was raised if it might be possible to pool some controlled results of study 228 along with the pooled laboratory and ECG results from the pool of patients in studies 168 and 169. Thus, depending on the time that is needed for you to resubmit the NDA, it may be possible to include data from the study 228 in the pooled analyses of laboratory and ECGs results.

- Provide a detailed Table of Contents (TOC) for each document showing page location of each section/subsection, and ALL tables, figures, and listings or other items AND a hyperlink to each item (section, subsection, table, figure, listing, or other item) in this detailed TOC. This TOC is requested in addition to bookmarks.

Efficacy

- Provide separate statistical analyses from 24 hour diary data showing the total number hours of sleep, and total number of hours "ON" with troublesome dyskinesia at the different times as well as change from baseline for these parameters throughout study 169 (i.e. from baseline through various post-treatment times until the end of the study).

Vital Signs (VS)

- For studies 168 and 169 provide separate analyses of VS, according to dose (up to 8 mg/d, > 8 -16 mg/d, > 16-24 mg/d, and any dose). The DNP believes that these data analyses will be more sensitive for detecting and characterizing treatment effects on blood pressure and pulse. These analyses should include: 1) absolute VS data over time; 2) VS change from baseline over time; and VS outlier analyses. Supportive listing data for individual patients should also be provided.
    - The DNP will provide desired tables for various VS analyses, especially for outlier analyses. The data can be inserted into these tables.

- Pool VS analyses for studies 168 and 169 (and 228 if unblinded data are available) according to treatment group and dose (described above).

- In the ISS, present appropriate VS analyses of central tendency (including change from baseline), and outlier analyses and discuss these findings across studies in an integrative manner.

- Please specify in the ISS the studies in which orthostatic vital sign (VS) data were collected and those in which the data were collected 4 hours after dosing. Please also note if data for specific studies were collected at random times after dosing. It does not appear that orthostatic VS were collected immediately prior to dosing for comparison of the change at 4 hours. If you are able to document that patients had VS collected at 4 hours after dosing, please summarize how frequently (%) these data were collected at this timepoint (within a window, such as $\pm$ 30 minutes). If you are unable to document compliance, please note this.

- Please provide detailed analyses of frequency of outlier results (using DNP outlier tables and outlier criteria) for study 167 in which VS were monitored at specified times (e.g. 1, 2, 3, 4 hrs) post-dosing over 4 weeks

- Please revise study 167 data presentation for change from pre-dosing for semisupine to standing positions. These data are calculated and shown as "semisupine minus standing" but should be calculated and shown as "standing minus semisupine."

Clinical Laboratory Results

- There were no analyses of analyte values over time, analyte change from baseline or shift analyses of analytes in the individual, pivotal study reports (168, 169). Although such analyses are typically expected in an NDA, the only laboratory analyses that were provided in these pivotal studies were the frequency of laboratory abnormalities of clinical concern.

- The requested analyses should include : 1) absolute central tendency of laboratory data over time; 2) central tendency of laboratory data change from baseline over time; 3) laboratory data shift analyses (outside the "normal" reference range) over time; and 4) laboratory data outlier analyses (separate analyses for outside the "normal" reference range and for marked abnormalities of clinical concern). Supportive listing data for individual patients should also be provided.
  - Please present the separate incidence of outlier abnormalities according to treatment for "abnormal" results (i.e. outside the "normal" reference range) and for marked abnormalities of clinical concern. These incidence analyses should be conducted for the whole study, the titration phase, and the maintenance phase according to the guidelines recommended for analyzing TEAEs in the titration or maintenance phases.

- Please also present pooled laboratory data analyses for studies 168 and 169 (and 228 if unblinded data are available) according to treatment group as requested for the separate analyses of studies 168 and 169.

- In the ISS, present appropriate laboratory data analyses of central tendency (including change from baseline), shift analyses, and outlier analyses and discuss these findings across studies in an integrative manner.

- The DNP has provided recommended criteria (see attached list) for the definition of laboratory outlier results ("critically abnormal") of clinical concern to be applied to the results in studies 168 and 169 and pooled analyses in the ISS.

ECGs

- For studies 168 and 169, please provide separate ECG analyses according to dose (up to 8 mg/d, > 8 - 16 mg/d, > 16-20 mg/d, > 20-24 mg/d, and any dose). The DNP believes that these data analyses will be more sensitive for detecting and characterizing treatment effects.

- The submitted analyses should be conducted according to treatment (and dose) and should include: 1) absolute central tendency of ECG parameters over time; 2) central tendency of ECG parameter change from baseline over time; and 3) ECG parameter outlier analyses. Supportive listing data for individual patients should also be provided.

- Please also present pooled laboratory data analyses for studies 168 and 169 (and 228 if unblinded data are available) according to treatment group and dose (described above) as requested for the separate analyses of studies 168 and 169.

- In the ISS, present appropriate ECG parameter analyses of central tendency (including change from baseline), shift analyses, and outlier analyses and discuss these findings across studies in an integrative manner.

TEAEs of Special Interest:

- The DNP recommends expanding the list of TEAEs of Special Interest. Your list of TEAEs of special interest included: hypotension/orthostatic hypotension, syncope, hallucinations, sleep attacks, melanoma, and events suggestive of retinal dysfunction, relevant fibrotic complications, and QTc prolongation. The DNP recommends adding other events to the list of TEAEs of special interest. These items include events suggestive of: compulsive behavior consisting of pathological gambling or hypersexuality, "falls," cardiac arrhythmia (particularly Torsades des pointes or any ventricular tachycardia/fibrillation), withdrawal-emergent hyperpyrexia and confusion (from study treatment reduction or withdrawal).

- Significant deficiencies concerning TEAEs of special interest in the initial NDA submission related to the presentation and analyses of these events. It was not clear which specific AE terms comprised the list of comprehensive AE terms that were used to search the database to identify possible cases that might represent the TEAE of special interest. Neither was it clear that once a possible case of a TEAE of special interest was identified, what case definition was used to include or exclude that patient from being listed as a patient with the TEAE of special interest. The DNP notes that you followed a DNP desired approach when you conducted more comprehensive analyses of the safety database for possible cases of fibrotic complications in your RLS NDA for IR-ropinirole.

    - Compile a comprehensive, broad list of AE terms that might be used to identify a possible case of a TEAE of special interest for all patient studies.

    - Provide a case definition for each event of special interest and apply the case definition to each of the possible cases identified from the search of the database using the comprehensive, broad list of AE terms. This procedure will identify cases that meet the definition for the TEAE of special interest.

    - Present the narratives (see DNP detail recommendations relative to narratives) for all cases of each TEAE of special interest. If there is an extraordinarily large number of cases identified for one or more TEAEs of special interest, please contact DNP for further advice.

    - Present the incidence, total number of events, and total number of patients for events that may have been suggestive of a TEAE of special interest separately for controlled and open-label experience.

    - In the ISS, discuss in an integrative manner the results across studies for the analyses of cases meeting the definition of a TEAE of special interest. In particular, please focus on discussing the frequency according to treatment and dose, the onset during the titration and maintenance phases, and whether serious. Whenever a specific case is discussed in the ISS, please provide a hyperlink to the narrative.

    - The DNP provides an example of how one might analyze for "falls." AE terms (e.g. some examples but not a complete list) that might be included in this search are fall, abrasion,

laceration, fracture, hematoma (any type), ecchymosis, joint sprain, head injury, and limb injury NOS, and crush injury to a limb. You should consider such events possibly suggestive of a fall unless there is information to suggest that the event was not a result of a fall.

Analyses of Post-Marketing Safety Experience

- Your summary presentation of the post-marketing safety of ropinirole was extremely brief and limited in scope despite marketing of this drug for nearly 10 years. It was not possible to have any significant comprehension of this experience from the initial marketing up to the time of the NDA submission, particularly with respect to the list of many TEAEs (including your list and the DNP expanded list) of special interest.

- Please provide a comprehensive integrative review of the post-marketing safety experience globally for ropinirole since the first approval. Please also pay particular attention to the revised, DNP recommended list of TEAEs of special interest.

Not Specifically Discussed

- Submit the study report for the study in which you prospectively conducted detailed ophthalmological monitoring investigating the effect of ropinirole for possible retinal toxicity.

- Were there any manual audits conducted of the automated, computer coding procedure (for MedRA) of verbatim AE terms to preferred terms to ensure that the translated coding was clinically accurate and reasonable? In studies in which automated coding of verbatim terms to preferred terms was initially conducted according to WHOART but then there was recoding using MedRA, did the recoding procedure recode WHOART preferred terms to MedRA preferred terms or verbatim terms to MedRA preferred terms? If you want to combine AE analyses across studies, it seems that the same coding procedure should be followed for all studies such that verbatim terms are coded to preferred terms using MedRA.

- Include the adverse event coding dictionary as a PDF file.

- In regard to definition of serious adverse events (SAEs), you noted that "variations in criteria exist across studies in this development programme." You should address in the ISS what were the specific differences in the specific studies and why there should not be any significant concerns because of these different definitions used for SAEs.

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

/s/

Russell Katz
4/21/2006 08:28:25 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-008

SmithKline Beecham Corporation
d/b/a/ GlaxoSmithKline
Attention: Elizabeth A. McConnell, Pharm.D.
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

Dear Dr. McConnell:

We received your February 17, 2006 correspondence on February 17, 2006 notifying us that you are withdrawing your new drug application (NDA) for Requip XL (ropinirole hydrochloride) Extended Release Tablets 2 mg, 3 mg, 4 mg, and 8 mg prior to its filing date.

In accordance with 21 CFR 314.65, this application is withdrawn as of February 17, 2006. If you have paid a user fee, we will refund 75% of your payment.

If you decide to resubmit this application, this withdrawal will not prejudice any future decisions on filing. You may reference information contained in this withdrawn application in any resubmission. However, because we retain only the archival copy of a withdrawn application in our files, you should resubmit appropriate review copies of all information. Retain the above NDA number for the resubmitted application but obtain a new user fee identification number. The new user fee identification number must be on the check as well as on the User Fee Cover Sheet in the resubmitted application. Submit the check for the appropriate user fee to the following address:

Food and Drug Administration
P.O. Box 360909
Pittsburgh, PA 15251-6909

For courier delivery, write the NDA number, the FDA Post Office box number (P.O. Box 360909), and the user fee identification number are the check and deliver it to the following address:

Food and drug Administration (360909)
Mellon Client Service Center, Room 670
500 Ross Street
Pittsburgh, PA 15262-0001

In addition, the resubmitted application should address the following deficiencies identified before receipt of your withdrawal request:

Nonclinical

You propose a specification of not more than (NMT) —— for ——impurity, ———— ———————— in your drug product that exceeds the qualification threshold for impurities in drug products (cf. Guidance for Industry Q3B(R) Impurities in New Drug Products November 2003 ICH Revision 1). You have submitted only a 14-day oral toxicity study in mice (Study TP-1008/SKF-101468/1) to support the specification level you propose; this is inadequate. To adequately qualify an impurity in a drug product intended for chronic oral use in humans, you would need to conduct (at a minimum) a 90-day oral toxicity study in one species (with justification provided for selection of species) and an assessment of genotoxic potential (i.e., a bacterial reverse mutation assay and either an in vitro chromosomal aberration assay in mammalian cells or an in vitro mouse lymphoma tk assay (with colony sizing)). Alternatively, you may choose to lower the specification level for this impurity to the qualification threshold or below (i.e., ≤0.5%). b(4)

Problems with Navigability within the NDA

1. There is no table of contents for the large, separate document (445 pages) that contains the Safety Summary Data Source Figures and Tables and is located in module 5 (i.e. module 5-m5.3.7.5). One can hyperlink to these data in module 5 from the Clinical Summary of Safety (CSS) in module 2; however, when one goes to this document (module 5-m5.3.7.5), one cannot find a stand alone table of contents showing the names of tables and figures that are contained in the m5.3.7.5 document or the specific page location of these tables and figures without "paging" through all 445 pages. It is not sufficient to have only electronic bookmarks in the margin for such a document instead of a stand alone table of contents. Electronic bookmarks cannot be printed and are not conducive to easily identifying names of tables and figures, many of which are long and similar except for a word or few words at the end of the long name.

2. It is difficult to find specific information about possible cases of interest in your section entitled Adverse Events of Special Interest (2.1.5.2 in the CSS) and its various inclusive sections (e.g. Hypotension/orthostatic hypotension, Syncope, Hallucinations, Sleep Attacks). In most instances, these sections did not identify or discuss specific patients but typically only summarized some information about patients. When such cases/patients were identified by a patient ID # in these sections, there was no hyperlink to the specific patient or to a narrative of the patient in the final study report that presumably contained specific information about the patient and the adverse event of interest. There was no consistent opportunity to hyperlink to narratives of all patients included in these sections. Only rarely was it possible to hyperlink to narratives of specific patients included in these sections.

3. It was not possible to hyperlink to information and narratives about specific patients included in Appendix 1 which is an important 12 page tabular listing of over 250 patients (showing patient ID, study #, treatment, preferred term for AE/SAE) who experienced a SAE, AE leading to study discontinuation, or AE of special interest. You frequently referred to Appendix 1 in your section Adverse Events of Special Interest (2.1.5.2 in the CSS), but it was not possible to hyperlink to information about a specific patient to learn about these specific cases/patients described in this Appendix without manually going to the final study report and then manually searching for this information. In general, it is very difficult navigating through the NDA to learn about specific information of patients of potential interest for their adverse reactions.

4. The narratives for SAEs are scattered throughout all of the individual Clinical Study Reports and are not grouped together in a single location as are the narratives that you grouped together for patients who discontinued for an adverse event. Providing all narratives in a single location within an NDA in conjunction with a summary listing of all patients (for which a narrative is provided), the adverse

event experienced, and specific page location and hyperlink to the narrative significantly facilitates the review of these narratives.

5. You did not submit an Integrated Summary of Safety (ISS) or an Integrated Summary of Efficacy (ISE). A recent ICH Guidance (M4: The CTD -- General Questions and Answers - Issued 12/04, Posted 12/22/2004) specifically notes that: "The ISS/ISE are critical components of the safety and effectiveness submission and are expected to be submitted in the application in accordance with the regulation. FDA's guidance *Format and Content of Clinical and Statistical Sections of Application* gives advice on how to construct these summaries. Note that, despite the name, these are integrated analyses of all relevant data, not summaries." This Guidance further notes that "The CTD Clinical Overview and Summary in Module 2 will not usually contain the level of detail expected for an ISS." In particular, the Clinical Summary of Safety (CSS) that you submitted does not comprehensively take an integrated approach to safety analyses but mostly summarizes results from individual Clinical Study Reports or refers the reader to these individual reports. Neither does your CSS contain the level of detail that we ordinarily see and ordinarily would expect in a complete ISS.

6. Your NDA submission did not contain a comprehensive analysis of Post-Marketing Data derived from the 10-year marketing experience with immediate release ropinirole. In your CSS, you presented a brief, 3 paragraph summary about your Post-Marketing experience with ropinirole but you not did not provide any specific information to review particularly for adverse reactions described in the Warnings and Precautions sections of your label or for other adverse reactions of special interest (e.g. pathological gambling, QTc prolongation/arrhythmia particularly ventricular tachycardia or Torsade des pointes, adverse events suggestive of falls).

7. Finally, we have also identified numerous other problems/concerns/deficiencies relative to: 1) the absence of particular analyses that we ordinarily would expect to be submitted with the NDA or that we ordinarily would request (at a pre-NDA meeting); or 2) the adequacy of many analyses contained in your NDA. We plan to compile a list of the analyses that should have been submitted or were submitted and are considered inadequate and will provide this information to you in a separate communication.

If you have any questions, call Teresa Wheelous, Sr. Regulatory Management Officer, at (301) 796-1161.

Sincerely,

{See appended electronic signature page}

Russell Katz, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Russell Katz
2/17/2006 03:02:40 PM

MEETING MINUTES

DATE: **February 6, 2003**

TIME: **1 PM**

LOCATION: **WOC II Conference Room E**

APPLICATION: **IND 60503 Requip Oral controlled Release Tablets for Parkinson's Disease**

TYPE: **End of Phase 2**

ATTENDEES

FDA

NAME	TITLE & DIVISION
Dr. Russell Katz	Division Director HFD-120
Dr. Janeth Rouzer-Kammeyer	Medical Reviewer HFD-120
Dr. Sally Yasuda	Clinical Pharmacology & Biopharmaceutics Reviewer HFD-860
Dr. Ramana Uppoor	Clinical Pharmacology & Biopharmaceutics Team Leader HFD-860
Dr. Sharon Yan	Biometrics Reviewer HFD-710
Ms. Stephanie Johnson	Pharmacy Student, Visiting
Ms. Teresa Wheelous	Senior Regulatory Management Officer

GLAXOSMITHKLINE REPRESENTATIVES

NAME	TITLE
Nancy Earl, MD	Group Director, Neurology Clinical Development
Marc Risner, PhD	Sr. Director, Neurology Clinical Development
Reijo Salonen, MD, PhD	Vice President Neurology and GI Clinical Development
Chrysa Mahoney	Neurology Clinical Development
Mr. James Murray	Vice President, Regulatory Affairs, Psychiatry and Neurology
Elizabeth McConnell, Pharm.D	Associate Director, Regulatory Affairs, Neurology
Debbie Tompson	Sr. Clinical Pharmacokineticist, Clinical Pharmacology and Discovery Medicine
Julia Statham, PhD,	Statistics
Neda Rashti	Clinical Program Manager, SkyePharma

BACKGROUND:

The immediate release formulation of ropinirole was approved on September 19, 1997 NDA 20-658, and is dosed three times a day. An end of phase 2 meeting request dated Dec. 12, 2002 was submitted and granted on Dec. 30, 2002. The meeting package dated January 10, 2003 was received on January 13, 2003.

DISCUSSION QUESTIONS:

CLINICAL

Clinical Studies (Section 6.2)

Will the proposed, single Phase III clinical study in advanced Parkinson's Disease patients be sufficient to support approval of ropinirole CR for patients with all stages of Parkinson's Disease

Yes. (There was some discussion about whether requiring a study in advanced PD vs. early PD would represent a higher or a lower hurdle to meet.) There was, additionally, considerable discussion about the food effect on ropinirole and the implications of this for extending the results from the planned adjunctive study to the monotherapy setting. Numerous ways of addressing this concern were discussed, to include not requiring that ropinirole be taken with food and collecting data on the timing of drug intake in relation to food intake.

STUDY 169

Eligibility Criteria and Assessments (Section 6.3.2)

Does the Agency agree that a minimum of two hours awake time "off" during the placebo run-in period is an appropriate eligibility requirement?

- The Division responded that we would like to see a greater minimum than two hours awake time "off". DNDP also expressed a preference for a 2-week placebo run-in period as opposed to a 1-week placebo run-in period. A longer run-in period will provide a more stable baseline result.

Does the Agency agree that recording in a diary for two days per week prior to each visit is sufficient to assess awake time "off"?

- Yes. Dr. Yan questioned whether there might be a selection bias regarding which 2 days are selected for recording. The protocol should specify which 2 days are selected for recording and be consistent.

Dosing and Titration of Ropinirole CR (Section 6.3.3)

Does the Agency agree that the proposed dosing guidelines (Table 2) are acceptable?

- The Division concurred.

Reduction of L-dopa (Section 6.3.4)
The current study design proposes that a required reduction in L-dopa start at a dose of 8 mg/day study drug (or matching placebo). Does the Agency agree that this will allow GSK to bridge to the previous IR adjunctive study, in which reduction in L-dopa was required once patients reached 7.5 mg/day study drug (or matching placebo)?

- This study (169) will stand on its own.

- The Division likes mandatory reduction in L-dopa, as it serves to standardize studies.

Down-titration of Ropinirole CR (Section 6.3.5)
Is the proposed one week down-titration schedule acceptable to the Agency?

- Yes, the proposed one week down titration schedule is acceptable.

Efficacy (Section 6.3.6)
Are the efficacy assessments proposed for the Phase III study acceptable to the Agency? Does the Agency agree that a reduction of 1.2 hours in awake time "off" is acceptable to demonstrate a clinically relevant difference between the ropinirole CR and placebo groups?

- Yes.

- The primary efficacy endpoint is the reduction in awake time "off" which will be analyzed by calculating the absolute change from baseline in awake time "off" within each treatment group. A responder analysis, defined as a patient with >20% reduction in awake time "off" and at least 20% reduction in L-dopa dose, will also be conducted.

- The firm proposes to use the UPDRS motor score as a secondary efficacy variable.

- The Division did note that converting "off" time to "on time with dyskinesias" is not necessarily a desirable outcome. The sponsor should look for this possibility.

Safety (Section 6.3.8)
Are the proposed safety assessments for the Phase III study acceptable to the Agency? Does the Agency agree with the proposed blood pressure measurements for Study 169?

- We want to see vital signs at maintenance and at 4 hr post dose.

Use of Ropinirole IR Safety Data to Support the Safety of Ropinirole CR in Parkinson's Disease (Section 6.61)
Does the Agency agree on the use of safety information from clinical trials with ropinirole IR to support safety information obtained from clinical trials with ropinirole CR?

- Yes, as long as nothing unexpected shows up in the CR trials.

CLINICAL PHARMACOLOGY

Selected Questions from the Sponsor:
Are the completed and planned studies characterizing the pharmacokinetic profile of ropinirole CR sufficient to support approval?

- Phase I and Phase II studies have evaluated or will evaluate bioavailability of CR (the final commercial formulation) compared to IR after single doses at lower strengths and at steady state at the highest strengths. Dose proportionality will be evaluated using all strengths. A Phase I food effect study has been performed and a Phase II food effect study at the highest strength at steady state is proposed. In addition, population PK studies will be performed at steady state at the highest doses. These studies should be sufficient to file the NDA, with respect to the requirements for bioavailability.

- Comments regarding specific studies are as follows:
    1) In Study 165 (dose proportionality study) it would be useful to evaluate blood samples on the 2 days prior to the PK days to assess whether steady state has been achieved.
    2) For the population PK studies (Studies168 and 169): It would be useful to obtain PK samples between 8 and 24 hours (such as 12, 16, and 20 hours) to evaluate the elimination phase. The sponsor stated at the meeting that this is practically difficult. Therefore, they will do model building from PK data in patients from studies 164 and 165, and then evaluate the PK in these pivotal clinical studies.

- It would be useful, in assessing efficacy and PK data, to obtain information from patient diaries regarding the time of dosing with respect to meals, especially since food enhances ropinirole CR bioavailability.

- It would be useful to obtain plasma samples at the time of adverse events.

- Consider using specific "windows" for timing of PK assessments, for both morning and afternoon samples, to ensure that not all samples are collected at the same time. This should be unified across all study centers.

- It may be useful to collect pharmacodynamic information during the down-titration phases to get a time course for off-set of effect.

- More detail is desirable in the population PK analysis plans. The sponsor should submit a detailed population PK plan to the agency for further evaluation.

- For population PK studies in the future, please simulate PK at steady state and provide simulations with respect to times for population PK assessments in the proposed protocol.

- In addition, we would recommend that you conduct a food effect study to evaluate the effect of different types of meals (fat content) on the PK profile of Requip CR. This

information, in combination with the data from the study in the presence of the high fat diet, as well as information from patient diaries in the clinical studies, may provide information that will be useful in the proposed labeling. The Sponsor proposed to use information from study [redacted] to address this issue. If the magnitude of food effect with the high fat meal in this steady state study is not comparable to the previous single dose study, another study may be considered.

b(4)

- Dissolution profiles and test methodology should be appropriately developed and dissolution data in multiple pH media for all strengths should be provided in the NDA.

Are the proposed safety assessments for the Phase III study acceptable to the Agency?

- Prolongation of the QTc interval on the ECG (QTc > 500 msec) was noted with low doses of both IR and CR ropinirole, in 1 patient each, in Phase II Study 166. At the meeting of February 6, 2003 the Sponsor agreed to look more closely at the ECG data from the patients for whom QT prolongation was reported. Depending on the reliability of this signal and previous clinical data regarding potassium channel blockade, the Sponsor may consider closer monitoring of QT interval in the Phase II studies. Depending on those results, it may be necessary to do more frequent monitoring in Phase III.

Will the pharmacokinetic data generated in Study 164 be adequate to establish the relative bioavailability of ropinirole CR vs. IR, and to provide directions for use in labeling for switching from IR to CR dosing?

- Study 164 appears to be adequately designed to establish bioavailability of CR ropinirole relative to IR ropinirole, at steady state at the highest strength of CR ropinirole. Trough concentrations on 2 consecutive days prior to the pharmacokinetic study day should be collected to assess the achievement of steady state. In addition to Cmax and AUC, the point estimates and 90% confidence intervals should be derived for the ratio of CR to IR for Cmin.

- Study 164 along with the results from Study 168 should provide for information regarding switching from IR to CR dosing at several doses.

- One concern regarding switching from IR to CR in practice is that the current IR label states that IR can be taken without regard to meals, although food reduces the Cmax of IR. The proposed studies evaluate switching when both IR and CR are taken with meals. If IR is taken without meals in practice, and patients are switched to CR, it is possible that the switching protocol may not be ideal.

We propose to conduct the steady state dose proportionality study in the fed state in order to mimic clinical practice. Will this approach be acceptable to address the modified release guidance for pharmacokinetic data at each tablet strength?

- Proposed Study 165, assessing dose proportionality in the fed state, is acceptable if this reflects the conditions that will be recommended in the proposed labeling.

Does the Agency agree on the use of safety information from clinical trials with ropinirole IR to support safety information obtained from clinical trials with ropinirole CR?

- Refer to QT consideration in question above. QT prolongation was not noted in the label for REQUIP.

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

/s/

Russell Katz
10/11/03 12:41:06 PM