CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-008

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	April 10, 2008
To:	Russell Katz, MD, Director Division of Neurology Products
Thru:	Kellie Taylor, PharmD, MPH, Team Leader Denise Toyer, PharmD, Deputy Director Carol Holquist, RPh, Director Division of Medication Error Prevention
From:	Jinhee J. Lee, PharmD, Safety Evaluator Division of Medication Error Prevention
Subject:	Medication Error Labeling Review
Drug Name:	Requip XL (ropinirole) Extended-release Tablets
Application Type/Number:	NDA 22-008
Applicant:	GlaxoSmithKline
OSE RCM #:	2008-349

CONTENTS

EXECUTIVE SUMMARY

The Division of Medication Error Prevention reviewed the applicant's responses to the recommendations made in a December 7th e-mail about their submitted container labels and carton labeling. For the most part, we were in agreement with their responses, but also had a few additional comments. We also reviewed the container labels and carton labeling and noted that improvements could be made to the container labels and carton labeling to decrease the potential for selection errors and to increase readability of information presented on the labeling. For full recommendations, we refer you to section 5 of this review.

1 BACKGROUND

1.1 INTRODUCTION

This memorandum is in response to a February 1, 2008 request from the Division of Neurology Products for a review of the applicant's response to our labels and labeling comments. We note that the applicant stated in their letter to the Division that the container labels and carton labeling have been revised.

The Division of Medication Error Prevention originally reviewed the container labels and carton labeling and forwarded comments to DNP in an e-mail on December 7, 2007.

1.2 PRODUCT INFORMATION

Requip XL is an extension to the applicant's Requip product line. However, unlike Requip which is indicated for both Restless Legs Syndrome and Parkinson's disease, Requip XL is only indicated for the treatment of Parkinson's disease. Requip XL is formulated as a three-layered tablet with a central, active-containing, slow-release layer, and 2 placebo outer layers acting as barrier layers which control the surface area available for drug release. The recommended starting dosage is 2 mg taken once daily for 1 [redacted] Requip XL will be supplied as 2 mg, 3 mg, 4 mg, and 8 mg tablets. b(4)

2 METHODS AND MATERIALS

This section describes the methods and materials used by the Division of Medication Error and Prevention medication error staff conducting a label, labeling, and/or packaging risk assessment (see section 3 Results). The primary focus for the assessment is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [1]

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The carton and container labels communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

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[1] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors.html. Last accessed 10/11/2007.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.[2]

Because the Division of Medication Error Prevention staff analyze reported misuse of drugs, the Division of Medication Error Prevention staff are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. The Division of Medication Error Prevention uses FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

For this product the Sponsor submitted on February 1, 2008 the following labels and insert labeling for the (see Appendices A, B, C, D for images)

- Retail Container: 2 mg, 3 mg, 4 mg, 8 mg
- Sample Container: 2 mg (21 tablet package)

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The Division of Medication Error Prevention compared the revised labels to both the current and previously proposed labels to identify any outstanding areas of concern from a medication errors perspective. We note that there were some recommendations that were overlooked in the previous review that we would like to bring to attention in this one. These recommendations represent new areas of concern from a medication errors perspective and are noted below. In addition, we will comment on the applicant's responses, if any, below.

3 RESULTS

The Division of Medication Error Prevention notes that the revised labels and labeling are generally consistent with the requests and comments forwarded to the applicant on December 7, 2007. However, we have identified some new and outstanding areas of concern.

3.1 RESPONSE TO APPLICANT'S COMMENTS

The Division of Medication Error Prevention acknowledges that the applicant has changed the established name from ropinirole hydrochloride to ropinirole. We also note that the applicant proposed to extend those changes to their prescribing information.

The Division of Medication Error Prevention agrees that the Requip XL 8 mg label and the Requip 0.5 mg label do not resemble each other.

The Division of Medication Error Prevention acknowledges that the applicant has enlarged the NDC numbers on all the labels and labeling.

The Division of Medication Error Prevention acknowledges that the 21 CFR 201.20(c) has been suspended pending further action, and agrees that the listing of inactive ingredients in the package insert is adequate.

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[2] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

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_____ Deliberative Process (b5)

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/s/

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5/28/2008 09:04:49 AM
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Department of Health and Human Services
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Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	January 18, 2008
To:	Russell Katz, MD, Director Division of Neurology Products
Thru:	Kellie Taylor, PharmD, MPH, Team Leader Denise Toyer, PharmD, Deputy Director Carol Holquist, RPh, Director Division of Medication Errors and Technical Support
From:	Jinhee J. Lee, PharmD, Safety Evaluator Division of Medication Errors and Technical Support
Subject:	DMETS Labeling Review
Drug Name:	Requip XL (ropinirole) Extended-Release Tablets
Submission Number:	N/A
Application Type/Number:	NDA#: 22-008
Applicant/applicant:	GlaxoSmithKline
OSE RCM #:	2007-2551

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1/18/2008 04:36:32 PM
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1/18/2008 04:39:40 PM
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	January 18, 2008
To:	Russell Katz, M.D., Director Division of Neurology Products
Through:	Jodi Duckhorn, M.A., Team Leader Patient Labeling and Education Team Office of Surveillance and Epidemiology
From:	Sharon R. Mills, BSN, RN, CCRP Patient Product Information Specialist Patient Labeling and Education Team Office of Surveillance and Epidemiology
Subject:	OSE Review of Patient Labeling (Patient Package Insert)
Drug Name(s):	Requip XL (ropinirole hydrochloride) Extended-Release Tablets
Application Type/Number:	NDA #22-008
Applicant/sponsor:	GlaxoSmithKline
OSE RCM #:	2007-2551

1 INTRODUCTION

The sponsor received original approval for Requip (ropinirole hydrochloride) under New Drug Application (NDA) #20-658 on September 19, 1997. The currently approved labeling is dated May 4, 2005. Requip (ropinirole hydrochloride) is indicated for the following:

Parkinson's Disease: REQUIP is indicated for the treatment of the signs and symptoms of idiopathic Parkinson's disease.

Restless Legs Syndrome: REQUIP is indicated of the treatment of moderate-to-severe primary Restless Leg Syndrome (RLS).

The approved labeling includes patient labeling in the form of a two-sided Patient Package Insert (PPI). One side addresses patient information for patients with RLS, and the other side addresses patient information for patients with Parkinson's Disease. OSE reviewed the patient labeling for REQUIP on December 16, 2003 and February 14, 2005. OSE additionally reviewed a Communications Research Study for Requip on April 21, 2005.

The sponsor submitted a New Drug Application, NDA #22-008 for REQUIP XL(ropinirole hydrochloride) Extended-Release Tablets on December 22, 2005, for the proposed indication: "for the treatment of signs and symptoms of idiopathic Parkinson's disease. The submitted labeling includes a Patient Package Insert for REQUIP XL for the Treatment of Parkinson's Disease. The review division took an Approvable action on December 7, 2007. The sponsor submitted a Complete Response to the Approvable letter on December 17, 2007, which included revised labeling and agreement to Phase 4 commitments as requested by the Agency.

2 MATERIAL REVIEWED

We reviewed the revised proposed Professional Information submitted by the sponsor on December 17, 2007. Additionally we reviewed a document provided by the review division which compares the Agency version of the Patient Package Insert (PPI) dated November 30, 2007 to the sponsor's revised proposed PPI submitted on December 17, 2007.

3 DISCUSSION

[redacted]

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4 CONCLUSIONS AND RECOMMENDATIONS

- Generally, we recommend only on PPI for all Requip formulations. However, the OSE review of the Communications Research Study for Requip concluded "...Therefore, from a patient comprehension perspective, the sponsor's request to produce a two-sided sheet with separate indications for use appears acceptable. If the sponsor submits future requests for additional indications (resulting in more than two FDA-approved indications), the two-sided sheet would no longer be feasible and a PPI that discusses all indications for use would be recommended."

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- We used the currently approved REQUIP PPI for the Treatment of Parkinson's Disease as our base document and incorporated appropriate language from the document provided by the review division for REQUIP XL.
- Our revised PPI has a Flesch Kincaid Grade Level of 7.5 and a Flesch Reading Ease Score of 64.0. To enhance comprehension, patient materials should have a Flesch Kincaid Grade Level of 6th to 8th grade and a Flesch Reading Ease Score of at least 60% (60% corresponds to an 8th grade reading level).
- We have simplified the wording where possible, re-ordered some of the content, eliminated unnecessary or redundant information, and ensured that the PPI is consistent with the PI.
- Since much of the information also applies to the REQUIP PPI for Restless Leg Syndrome, we recommend that the appropriate parallel changes be incorporated into that PPI.
- In the section What is the most important information I should know about REQUIP and REQUIP XL, please clarify whether the language in the Hallucinations bullet is simultaneous or mutually exclusive. It is unclear whether the bullet should read as follows:

  "The chances of having hallucinations is higher in patients with Parkinson's disease who are elderly, taking REQUIP or REQUIP XL with _____ or taking higher doses of REQUIP or REQUIP XL."

  Or:

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_____. We cannot specifically locate the information in the PI that hallucinations are associated with higher doses of REQUIP or REQUIP XL. This information should be in the PI or it must be deleted from the PPI. The PPI must always be consistent with the PI.

- There are no Contraindications listed in the PI. Since the PI is in PLR format, the PPI section '[redacted] information on allergies[redacted] to the section "What should I tell my before taking REQUIP or REQUIP XL?"
- The list of ingredients in REQUIP and REQUIP XL has been added to the end of the PPI.
- All relevant future changes to the PI should be incorporated into the PPI.
- We will provide the review division with marked-up and clean copies of our revised PPI in Word. We recommend that you use the clean copy as the working document.

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Please let us know if you have any questions.

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