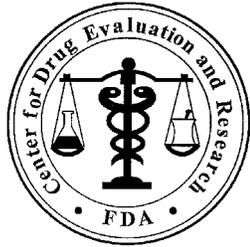


**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022377Orig1s000**

**OTHER 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: June 28, 2010

To: Russell Katz, MD, Director  
Division of Neurology Products

Through: Zachary Oleszczuk, PharmD, Acting Team Leader  
Denise Toyer, PharmD, Deputy Director  
Carol Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis

From: Felicia Duffy, RN, BSN, MSED, Safety Evaluator  
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name: Alsuma (Sumatriptan Injection)  
6 mg/0.5 mL

Application Type/Number: NDA 022377

Applicant: King Pharmaceuticals

OSE RCM #: 2010-94

**\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\***

## **INTRODUCTION**

This review summarizes DMEPA's evaluation of the revised Alsum (Sumatriptan) Injection container labels, carton and insert labeling, and instructions for use for areas that could lead to medication errors.

### **1.1 REGULATORY HISTORY**

DMEPA reviewed and provided recommendations for Sumatriptan labels and labeling in OSE review #2008-1340 dated May 12, 2009. On January 12, 2010, the Division of Neurology Products consulted DMEPA to review the revised labels and labeling submitted in the Applicant's December 23, 2009, electronic re-submission.

Regulatory history pertaining to the proposed names for this NDA was reviewed in OSE reviews #2008-1357 dated January 13, 2009, and #2008-1368 date April 7, 2009. The proposed names were found unacceptable. The Applicant proposed the proprietary name, Alsuma for this application which was found acceptable in OSE review #2010-637, dated June 4, 2010.

## **2 METHODS AND RESULTS**

### **2.1 LABELS AND LABELING**

Using Failure Mode and Effects Analysis (FMEA)<sup>1</sup> DMEPA evaluates the insert labeling and instructions for use (see Appendix C) submitted on December 23, 2009 and the container labels and carton labeling submitted on June 4, 2010 (see Appendices A and B).

## **3 CONCLUSIONS AND RECOMMENDATIONS**

We acknowledge the Applicant addressed our recommendations in OSE review #2008-1340. However, we noted additional areas where information on the labels and labeling can be improved to minimize medication errors. Section 3.1 *Comments to the Division*, contains our recommendations for the insert labeling. Section 3.2 *Comments to the Applicant*, contains our recommendations for the container labels, carton labeling, and instructions for use. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact Laurie Kelley, OSE Project Manager, at 301-796-5068.

### **3.1 COMMENTS TO THE DIVISION**

#### **A. Highlights of Prescribing Information and Full Prescribing Information (Dosage and Administration Section)**

The maximum recommended dose statement currently reads as follows: "The maximum recommended dose that may be given in 24 hours is two doses separated by at least 1 hour." This statement does not indicate the specific milligram dose to be administered. For clarity and to minimize medication errors, revise the maximum dose statement to include the milligram dose. For example: "The maximum recommended dose that may be given in 24 hours is two 6 mg doses separated by at least 1 hour."

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

## **B. Full Prescribing Information**

In Sections 2 (Dosage and Administration) and 17.5 (Patient Instructions for Use), the sentence “Since the injection is intended to be given subcutaneously, intramuscular or intravascular delivery must be avoided” is confusing as it refers to three different routes of administration (the intended route to be administered and two routes to be avoided). If this sentence is misinterpreted, this may lead to the administration of the drug by the wrong route. Revise this sentence to delete the two non-intended routes of administration and combine it with the very next sentence. The revised sentence should read “Since the injection is intended to be given subcutaneously, patients should be directed to use injection sites with an adequate skin and subcutaneous thickness to accommodate the length of the needle (e.g., lateral thigh or upper arm) [see Patient Counseling Information (17)]”.

## **C. Patient Package Insert**

In “How should I store Alsuma”, the first bullet is confusing because it contains excursion parameters. However, patients may not understand excursion or the storage parameters as currently presented. Please revise to use more patient friendly language.

### **3.2 COMMENTS TO THE APPLICANT**

#### **A. General Comments**

These comments pertain to all the labels and labeling. Please revise accordingly.

1. The product strength appears within the parenthesis in conjunction with the established name. Increase the prominence of product strength by relocating the established name so it appears beneath the established name and not in the parenthesis. Additionally increase the size of the strength.

#### **B. Container Label**

1. See General Comments.
2. Because the label is small, decrease the prominence of the distributor name in order to give more prominence to more pertinent information on the label.

#### **C. Carton Labeling**

1. See General Comments.
2. The distributor name and logo has greater prominence than the route of administration, therefore decrease the prominence of the distributor name in order to give more prominence to more pertinent information on the label.
3. Debold the phrase “Auto-Injector” as it appears more prominent than the established name. The phrase “Auto-Injector” should not have more prominence than the established name.

#### **D. Instructions for Use**

1. Revise all instances of the proprietary name to Alsuma.
2. Debold the phrase “Auto-Injector” as it appears more prominent than the established name. The phrase “Auto-Injector” should not have more prominence than the established name.
3. The Instructions for Use refer to the drug product as ‘your Alsuma’ or ‘the Alsuma’ which is somewhat confusing and difficult to read. In order to improve readability, either refer to the product as ‘Alsuma’ or ‘Alsuma auto-injector’. For example, the first sentence should be revised as:

‘Read the Patient Instructions for Use that come with Alsuma before you start using it and each time you get a refill’

OR

‘Read the Patient Instructions for Use that come with Alsuma auto-injector before you start using it and each time you get a refill’

#### **4 REFERENCES**

1. *OSE Review #2008-1340 dated May 12, 2009; Sumatriptan Usability and Labeling Review of Sumatriptan Injection; Duffy, Felicia.*
2. *OSE Review #2008-1357 dated January 13, 2009; (b)(4) Proprietary Name Review; Duffy, Felicia.*
3. *OSE Review #2008-1368 dated April 7, 2009; (b)(4) Proprietary Name Review; Duffy, Felicia.*
4. *OSE Review #2010-637 dated June 3, 2010; Alsuma Proprietary Name Review; Duffy, Felicia.*

4 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

2 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22377	ORIG-1	KING PHARMACEUTICA LS INC	SUMATRIPTAN SUCCINATE AUTO-INJECTOR

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

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/s/

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ZACHARY A OLESZCZUK  
06/28/2010

DENISE P TOYER  
06/28/2010

DENISE P TOYER on behalf of CAROL A HOLQUIST  
06/28/2010

**505(b)(2) ASSESSMENT**

<b>Application Information</b>		
NDA # 22-377	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: (b) (4) (b) (4)		
Established/Proper Name: sumatriptan		
Dosage Form: injection		
Strengths: 6mg/0.5ml		
Applicant: King Pharmaceuticals		
Date of Receipt: December 29, 2009		
PDUFA Goal Date: June 29, 2010	Action Goal Date (if different): (same)	
Proposed Indication(s): Migraine		

**GENERAL INFORMATION**

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES  NO

*If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*



**INFORMATION PROVIDED VIA RELIANCE  
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
NDA 20-080 Imitrex Injection	All except device usability study

\*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

Biowaiver for SQ injectable product, with supportive in vitro data.

**RELIANCE ON PUBLISHED LITERATURE**

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES  NO

*If “NO,” proceed to question #5.*

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES  NO

*If “NO,” proceed to question #5.*

*If “YES”, list the listed drug(s) identified by name and answer question #4(c).*

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES  NO

**RELIANCE ON LISTED DRUG(S)**

*Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.*

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES  NO

*If "NO," proceed to question #10.*

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Imitrex (sumatriptan) Injection	20-080	Y

*Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A  YES  NO

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".*

*If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES  NO

If "YES", please list which drug(s) and answer question d) i. below.  
If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES  NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a new pre-filled, single-use disposable auto-injector, that differs from the reference listed product with respect to design and operating principle.

*The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.*

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

**(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).**

**Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.**

YES  NO

If "**NO**" to (a) proceed to question #11.  
If "**YES**" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES  NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES  NO

If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES  NO

If "**NO**", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES  NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES  NO

If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in

*the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s):

**PATENT CERTIFICATION/STATEMENTS**

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): 5037845\*PED (Expired Feb 6, 2009)

No patents listed  *proceed to question #14*

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES  NO

*If "NO", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): 5037845\*PED

Expiry date(s): Feb 6, 2009

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR

314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

- (a) Patent number(s):
- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]? YES  NO

*If "NO", please contact the applicant and request the signed certification.*

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt. YES  NO

*If "NO", please contact the applicant and request the documentation.*

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

**Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES  NO  Patent owner(s) consent(s) to an immediate effective date of approval

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22377

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ORIG-1

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KING  
PHARMACEUTICA  
LS INC

-----  
SUMATRIPTAN SUCCINATE  
AUTO-INJECTOR

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/s/  
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LANA Y CHEN  
06/24/2010

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications**

**Memorandum**

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**\*\*PRE-DECISIONAL AGENCY MEMO\*\***

**DATE:** JUNE 23, 2010

**To:** Lana Chen  
Senior Regulatory Project Manager  
DNP

**CC:** Mary Dempsey  
Project Management Officer  
OSE, DRISK

LaShawn Griffiths  
Acting Team Leader  
OSE, DRISK

**From:** Sharon Watson, PharmD  
Regulatory Review Officer

**Subject:** Drug: Alsuma (sumatriptan) Injection  
NDA: 022377

---

DDMAC has reviewed the 06-08-10 version of the proposed Patient Labeling (PPI) from DNP and the 6-15-10 email memo from King Pharmaceuticals for Alsuma, and we offer the following comments. DDMAC's comments are provided directly on the 06-08-10 version of this document, attached below.

Thank you for the opportunity to comment on this proposed PPI.

If you have any questions or concerns regarding these comments, please contact me.

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS)  
immediately following this page

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22377

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ORIG-1

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KING  
PHARMACEUTICA  
LS INC

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SUMATRIPTAN SUCCINATE  
AUTO-INJECTOR

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SHARON M WATSON

06/23/2010



**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: June 8, 2010

To: Russell Katz, MD, Director  
**Division of Neurology Products**

Through: Mary Willy, Ph D, Deputy Director  
**Division of Risk Management (DRISK)**

LaShawn Griffiths, RN, MSHS-PH, BSN  
Patient Labeling Reviewer, Acting Team Leader  
**Division of Risk Management**

From: Robin Duer, RN, BSN, MBA  
Patient Product Labeling Reviewer  
**Division of Risk Management**

Subject: DRISK Review #2 of the Patient Labeling (Patient Package Insert, and Patient Instructions for Use)

Drug Name(s): TRADENAME (sumatriptan injection)

NDA # 22-377

Applicant/sponsor: King Pharmaceuticals, Inc.

OSE RCM #: 2008-1753

## **1 INTRODUCTION**

King Pharmaceuticals Inc. submitted a New Drug Application (NDA 22-377) for TRADENAME (sumatriptan injection) on July 16, 2008. The submission included proposed Professional Information (PI), with Patient Labeling information (Patient Package Insert, and Patient Instructions for Use). TRADENAME (sumatriptan injection) is indicated for the treatment of migraine and cluster headaches.

On May 11, 2009, the Division of Risk Management (DRISK) completed the review of the proposed patient labeling submitted on August 14, 2008 as requested by the Division of Neurology Products (DNP). On May 15, 2009 DNP issued a Complete Response (CR) letter for this NDA due to insufficient information about the drug to determine whether the product was safe for use. DRISK's proposed patient labeling changes were included with that letter. King Pharmaceuticals Inc. sent FDA a submission with revised labeling in response to the CR letter on December 23, 2009.

This review is written in response to a request by DNP for DRISK to review the Applicant's proposed Patient Package Insert (PPI) and Patient Instructions for Use (IFU) for TRADENAME (sumatriptan injection) submitted on December 23, 2009 in response to the CR letter.

Please let us know if DNP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant.

## **2 MATERIAL REVIEWED**

- Draft TRADENAME (sumatriptan injection) Patient Package Insert (PPI) and Patient Instructions for Use (IFU) submitted on December 23, 2009 and received by DRISK on May 24, 2010.
- Draft TRADENAME (sumatriptan injection) Package Insert (PI) submitted on December 23 2009, revised by DNP throughout the review cycle, and received by DRISK on May 27, 2010.
- DRISK review of the August 14, 2008 proposed TRADENAME (sumatriptan injection) patient labeling (Patient Package Insert, Patient Instructions for Use) dated May 11, 2009

## **3 RESULTS OF REVIEW**

In our review of the PPI and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the PI
- removed unnecessary or redundant information
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

Our annotated versions of the PPI and IFU are appended to this memo. Any additional revisions to the PI should be reflected in the PPI and IFU.

Please let us know if you have any questions.

23 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following

**505(b)(2) ASSESSMENT**

<b>Application Information</b>		
NDA # 22-377	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: (b) (4)		
Established/Proper Name: sumatriptan		
Dosage Form: injection		
Strengths: 6mg/0.5ml		
Applicant: King Pharmaceuticals		
Date of Receipt: July 17, 2009		
PDUFA Goal Date: May 17, 2009		Action Goal Date (if different): (same)
Proposed Indication(s): Migraine		

**GENERAL INFORMATION**

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES  NO

*If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*



**INFORMATION PROVIDED VIA RELIANCE  
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
NDA 20-080 Imitrex Injection	All except device usability study

\*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

Biowaiver for SQ injectable product, with supportive in vitro data.

**RELIANCE ON PUBLISHED LITERATURE**

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES  NO

*If “NO,” proceed to question #5.*

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES  NO

*If “NO,” proceed to question #5.*

*If “YES”, list the listed drug(s) identified by name and answer question #4(c).*

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES  NO

**RELIANCE ON LISTED DRUG(S)**

*Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.*

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES  NO

*If "NO," proceed to question #10.*

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Imitrex (sumatriptan) Injection	20-080	Y

*Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A  YES  NO

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".*

*If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES  NO

If "YES", please list which drug(s) and answer question d) i. below.  
If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES  NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a new pre-filled, single-use disposable auto-injector, that differs from the reference listed product with respect to design and operating principle.

*The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.*

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

**(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).**

**Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.**

YES  NO

If "**NO**" to (a) proceed to question #11.  
If "**YES**" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES  NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES  NO

If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES  NO

If "**NO**", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES  NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES  NO

If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in

*the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s):

**PATENT CERTIFICATION/STATEMENTS**

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): 5037845\*PED (Expired Feb 6, 2009)

No patents listed  *proceed to question #14*

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES  NO

*If "NO", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): 5037845\*PED

Expiry date(s): Feb 6, 2009

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR

314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

- (a) Patent number(s):
- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]? YES  NO

*If "NO", please contact the applicant and request the signed certification.*

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt. YES  NO

*If "NO", please contact the applicant and request the documentation.*

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

**Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES  NO  Patent owner(s) consent(s) to an immediate effective date of approval

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

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Lana Chen  
5/13/2009 02:36:19 PM  
CSO



**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: May 12, 2009

To: Russell Katz, MD, Director  
Division of Neurology Products

Through: Kellie Taylor, PharmD, Team Leader  
Denise Toyer, PharmD, Deputy Director  
Carol Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis

From: Felicia Duffy, RN, BSN, MEd, Safety Evaluator  
Division of Medication Error Prevention and Analysis

Subject: Sumatriptan Usability Study and Labeling Review

Drug Name: (Sumatriptan) Injection

Application Type/Number: NDA 22-377

Applicant: King Pharmaceuticals

OSE RCM #: 2008-1340

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## EXECUTIVE SUMMARY

This review is written in response to a request from the Division of Neurology for an evaluation of the usability study and labels and labeling for NDA 22-377 (sumatriptan injection) auto-injector. The application is identical to the currently marketed Imitrex injection; except that the medication is contained within a pre-filled auto-injector similar to the EpiPen device rather than the Imitrex StatDose device that requires assembly. As such, the Division of Medication Error Prevention and Analysis (DMEPA) considered the vulnerability of the delivery device and medication errors associated with EpiPen which may be indicative of potential errors with this submission.

Using Failure Mode and Effects Analysis<sup>1</sup>, DMEPA evaluated the container labels, carton labeling and insert labeling to identify vulnerabilities that could lead to medication errors. This auto-injector was previously studied in another application from the Applicant and revisions were made to both the device design and label based on the results of the previous studies in order to minimize the risk of needle-sticks. The revised device that minimized needle-sticks appears to have been studied in the application for this drug. DMEPA noted weaknesses in the methodology that may have affected the study results for this application. For example, the Applicant did not provide subjects with both the trainer device and the device with active drug (the manner in which the product will be packaged in the real world), nor did they use subjects naïve to pen devices. Although the usability study subjects reported ease of use and clear instructions for this NDA, we noted additional areas of needed improvement. These areas relate to the presentation of the established name, product strength, and route of administration on the container labels and carton labeling, and there is a need to further enhance the clarity of the instructions for use. (b) (4)

## 1 MATERIALS REVIEWED

For this product the Applicant submitted labels and labeling as part of the August 14, 2008 proprietary name submission (see Appendices A through E). The Applicant also submitted usability study K644-077-3001 which was reported on June 5, 2008 (see synopsis in Appendix F).

Since the auto-injector for this submission is similar to EpiPen, (b) (4) Regulatory history pertaining to the proposed proprietary names for this NDA was reviewed in OSE reviews 2008-1357 and 2008-1368. The proposed names were found unacceptable. To date, the Applicant has not submitted a new proprietary name, thus, we will refer to this product as “sumatriptan auto-injector” or “auto-injector” throughout this review.

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

## 2 REGULATORY HISTORY

In 2006, the Applicant submitted an IND an auto-injector containing diazepam (IND 61,477). During the clinical trials, three subjects sustained needle-sticks in which the Agency placed the IND on clinical hold. As a result of the clinical hold, the Applicant conducted a human factors study to research the factors that may have contributed to the accidental injections. As a result of the human factors study, the auto-injector was modified, and labeling was added to the auto-injector. The Applicant conducted three usability studies which supported the reduction in risk of accidental injections after the modifications. The final, less error-prone auto-injector as result of the usability study is the same auto-injector proposed for this NDA.

## 3 RESULTS AND DISCUSSION FOR USABILITY STUDY K644-07-3001

The Applicant submitted one clinical usability study to assess subcutaneous self-injection with sumatriptan using the proposed auto-injector. This study (K644-07-3001) was conducted to assess three items: 1) the successful subcutaneous self-injection with a single 6 mg dose of sumatriptan using the proposed auto-injector during a single migraine attack, 2) to compare the subcutaneous self-injection using the proposed auto-injector with the traditional self-injector device used to administer acute treatments for migraine, and 3) to assess the tolerability of the proposed auto-injector when used to treat a single migraine attack. DMEPA reviewed this study to determine what type of medication errors occurred during the study, and what the Applicant did in order to mitigate the errors that occurred, if any. We also evaluated the usability study to determine if the instructions for use were clear for the user, and how the labels, labeling, and/or device were revised to mitigate these errors. Postmarketing surveillance has shown that this type of pen device has reports of accidental needle-sticks because of patients putting their finger or thumb over the needle end of the device; therefore, we were especially concerned about the potential for needle-stick injuries during this study.

We note there are weaknesses in the Applicant's study population. The Applicant only used patients who had previously experienced migraine attacks and had effectively used injectable sumatriptan. Utilizing healthy naïve subjects (subjects naïve to migraines and without device experience) and migraine subjects who have not used an injectable device, would provide additional information on the usability of the device and the clarity of the instructions for use.

The Applicant did not indicate if revisions were made to the instructions for use, the container labels, or device as a result of the usability study. If there were any revisions, it does not appear that the revised container labels, instructions for use, or device were re-evaluated. Reassessing revisions would have helped to determine if the revisions mitigated or propagated potential errors. We can only infer that the instructions for use and container labels provided are the same that the study subjects used.

Lastly, the Applicant only provided the study subject with one auto-injector device. The proposed packaging configuration will contain two auto-injectors with active drug, (b) (4)

## 4 CONCLUSIONS AND RECOMMENDATIONS

Although the usability study has clear limitations in methodology, we did not identify any critical failures in the data submitted that would affect the approvability of this product. However, our evaluation noted areas where information on the container labels, carton labeling, and instructions for use can be improved to minimize the potential for medication errors. Section 4.1 *Comments to the Applicant* contains our recommendations for the container label, carton labeling, and instructions for use. We request these recommendations be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact Daniel Brounstein, Project Manager, at 301-796-0674.

### 4.1 COMMENTS TO THE APPLICANT

We have the evaluated your container labels, carton labeling, and instructions for use, and request you revise the following:

#### A. General Comments on the Container Labels and Carton Labeling

1. The word “Auto-Injector” appears next to the established name, sumatriptan succinate. Auto-Injector is a descriptor of the device and is not an approved USP dosage form. Thus, relocate the word Auto-Injector away from both the proprietary and established names (i.e., away from [TRADEMARK] Injection).

2.



3. The net quantity volume is not identified on the carton labeling or container label. Revise the product strength (6 mg) to include the volume in each injection (e.g., 6 mg/0.5 mL).

#### B. Container Label (Active drug)

1. The route of administration does not appear on the label. In accordance with 21 CFR 201.100 (b)(3), include the route of administration.
2. The order of important information on the labels and labeling is difficult to follow. Specifically, the proprietary name, established name, dosage form, and product strength are not presented in the usual format. Relocate the product strength from above the proprietary name to appear juxtapose to the established name and dosage form.

D. Carton Labeling

1. Include the route of administration statement on the principle display panel. We note that it is present on the side panel, but recommend that it also appear on the principal display panel in order to make this information more readily identifiable.
2. The order of important information on the labels and labeling is difficult to follow. Specifically, the proprietary name, established name, dosage form, and product strength are not presented in the usual format. Relocate the product strength so that it does not appear in the blue wave, but is juxtapose to the established name and dosage form.

E. Instructions for Use (Active drug)

1. The light green box holds important information (e.g. the blue safety release should not be removed until you are ready to use the auto-injector, the orange needle end should never be touched, etc.). As currently presented, the only statement that stands out is “Keep out of reach of children before and after use.” There are other important messages that need to be just as prominently displayed. The use of a light green colored text on a white background to highlight important information reduces the readability and is not very prominent. Improve the color contrast so that it is more prominent and will stand out to highlight important information to ensure users will read and not overlook this information before using the device (e.g., the Attention! box at the beginning of the instructions and other statements highlighted in light green in the instructions for use).

2. In the “How to Use” section, “Choosing an Injection Site” subsection, the user is instructed to



3. In the “How to Use” section, “Preparing the Auto-Injector” subsection, the second picture shows the auto-injector sliding into the user’s hand. We understand the intent of this graphic. However, when attempting this step, we believe the user will use their thumb or other part of the hand to stop the auto-injector when sliding into the hand. This contradicts the second bullet in “Holding the Injector”

section to “Never put the thumb on either end” of the auto-injector. In fact, in the picture shown, it appears as though the user is using their thumb at the blue cap on the injector. Revise the picture and/or directions to clarify these instructions.

4.



5. In the How to Use section, “Disposing of the Auto-Injector” subsection, the first step is to “Hold the auto-injector on a flat surface”. However, the picture shows the auto-injector being held in the air. Modify the picture and/or the situation to more explicitly convey what the patient should do in order to minimize the potential for needle-sticks.

6. In the “Storage/Disposal Case” section, the first bullet instructs the user to “Always store and carry the auto-injector in the storage/disposal case.”

(e.g., Always store and carry the [TRADEMARK] auto-injector in the storage/disposal case).

G. Package Insert

No comment.

H. Patient Package Insert

No comment.

3 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

## **Appendix F: Usability Study Synopsis**

The Applicant conducted one usability study (K644-07-3001). Subjects were followed through three visits. In visit 1, subject eligibility was confirmed, and subjects received training on the proper use of the auto-injector device by video instruction and a question and answer session with the study coordinator. Then each subject demonstrated proper administration of the auto-injector by using an active auto-injector on a paper towel roll. Subjects were enrolled and dispensed an auto-injector with one dose of sumatriptan. Subjects were provided with take-home questionnaires to record pre- and post-dose pain scores, and to provide an assessment of auto-injector. Visit 2 was conducted within 72 hours after a migraine for the treatment visit. Subjects brought in their take home questionnaires with their recorded data which included pre- and post-dose pain scores, and an assessment of the auto-injector. During visit 2, investigators performed a safety assessment, examined the injection site, confirmed successful administration of the sumatriptan through review of the subject diary, and reviewed the subject pain and auto-injector questionnaires. Visit 3 was a telephone follow-up conducted within 7-10 days post treatment with the auto-injector to record the use of any concomitant medications or adverse events that had occurred since visit 2.

K644-07-3001 contained 63 subjects who had prior effective use of subcutaneous injectable sumatriptan on at least two occasions within the previous two months for the treatment of migraines with or without aura. The study design required that subjects have a single dose administered during a migraine attack using the auto-injector. Successful administration of a 6 mg dose with the auto-injector was demonstrated by 1) subject questionnaire responses indicating injection into the arm or thigh during a migraine attack and 2) confirmation that auto-injector use through inspection by the Sponsor of the used auto-injector. Sixty-two of the 63 subjects (98%) successfully administered their injections. The one remaining subject's injection was counted as unsuccessful, despite the subject's report of a successful injection because the auto-injector was not returned and could not be confirmed by sponsor inspection as a success.

All 63 (100%) of subjects agreed that the written instructions were clear and easy to follow. Sixty subjects (95%) agreed or strongly agreed that the auto-injector was easy to use, and all 63 (100%) were able to self-administer the study treatment with no accidental injections according to subject diary reports. The one subject that deemed as having an unsuccessful injection did report diary information indicating success, but failed to return the auto-injector. Overall, 41 subjects (65%) preferred the new auto-injector, 14 subjects (22%) expressed no preference, and 8 subjects (13%) preferred the traditional self-injector device.

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this page is the manifestation of the electronic signature.**  
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/s/

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Felicia Duffy  
5/12/2009 04:58:50 PM  
DRUG SAFETY OFFICE REVIEWER

Carol Holquist  
5/12/2009 05:45:11 PM  
DRUG SAFETY OFFICE REVIEWER



**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: May 11, 2009

To: Russell Katz, M.D., Division Director  
**Division of Neurology Products**

Through: Jodi Duckhorn, MA, Team Leader  
**Division of Risk Management**

From: LaShawn Griffiths, MSHS-PH, BSN, RN  
Patient Product Information Reviewer  
**Division of Risk Management**

Subject: DRISK Review of Patient Labeling (Patient Package Insert)  
and (Patient Instructions for Use)

Drug Name(s): TRADENAME (sumatriptan) Injection

Application  
Type/Number: NDA 22-377

Applicant/sponsor: King Pharmaceuticals

OSE RCM #: 2008-1753

## 1 INTRODUCTION

King Pharmaceuticals submitted a New Drug Application (NDA 22-377) for TRADENAME (sumatriptan) (b) (4) injection on July 16, 2008. The submission includes proposed Professional Information (PI) in PLR format, with Patient Labeling Information (Patient Package Insert), and Instructions for Use (IFU). TRADENAME (sumatriptan) is indicated for the treatment of migraine and cluster headaches.

The Division of Neurology Products requested that the Division of Risk Management's Patient Labeling and Education Team review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU). This review is written in response to that request.

## 2 MATERIAL REVIEWED

- TRADENAME Patient Package Insert (PPI) submitted August 14, 2008
- TRADENAME Patient Instructions for Use (IFU) submitted August 14, 2008
- TRADENAME Prescribing Information (PI) submitted August 14, 2008 and revised by the Review Division throughout the current review cycle

## 3 DISCUSSION

The purpose of patient directed labeling is to facilitate and enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8<sup>th</sup> grade reading level). The reading scores for each of the documents as submitted by the Applicant and also with our recommended changes are indicated in section 4 below.

In our review of the PPI and IFU, we have:

- simplified wording and clarified concepts where possible,
- ensured that the PPI is consistent with the PI,
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We have reformatted the PPI document using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the PPI and IFU. Comments to the review division are ***bolded, underlined and italicized***.

We are providing the review division a marked-up and clean copy of the revised PPI and IFU. We recommend using the clean copy as the working document.

All future relevant changes to the PI should also be reflected in the PPI and IFU.

#### 4 CONCLUSIONS AND RECOMMENDATIONS

The proposed PPI and IFU were reviewed as separate documents because the proposed IFU was in PDF, the Applicant should put them back together for labeling and dissemination.

##### Tradename (sumatriptan) Patient Package Insert (PPI)

1. The Applicant's proposed PPI has the following readability scores:

- Flesch Reading Ease: 54.6%
- Flesch-Kincaid Grade Level: 9.1

The sponsor's readability scores for the PPI are higher than that recommended for optimal patient comprehension. We recommend that the sponsor simplify the PPI by incorporating our recommendations.

Our revised PPI has the following readability scores:

- Flesch Reading Ease: 51.3%
- Flesch-Kincaid Grade Level: 8.5

2. The Applicant use the term "doctor" and "healthcare provider" in the proposed PPI. We suggest that one term be used consistently throughout the PPI. We have chosen to use the term "healthcare provider" for the purposes of this review.

3. We deleted the sections (b) (4) (b) (4). The purpose of Patient Information is to enhance appropriate use and to provide important information to patients about medications. This disease specific information can be placed at the end of the PPI after the "Ingredients" section or preferably addressed with the patient separately from the product specific information.

4. The medications (b) (4) have been deleted from the "Who should not take" section because these medications have been discontinued.

5. In the section "What should I tell my healthcare provider before taking TRADENAME?" the term "overweight" is vague the Applicant should quantify an amount of what is considered to be "overweight".

6. In the section, "How should I take TRADENAME" we added the term "abdomen" as an appropriate injection site to the "Patient Counseling" section because it is listed as an injection site in the highlight section under "dosage and administration".

7. In the section "What are the possible side effects of TRADENAME", the Applicant should:

- clarify for the patient where the "feeling of heaviness" is located
- clarify for the patient where the (b) (4) is located
- clarify what "feeling strange" means

- specify where the muscle pain is located, for example, near the injection site or all over the body?
8. We have added the following statement to the end of the section, “What are the possible side effects of TRADENAME?”:
- Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.
- This verbatim statement is required for all Medication Guides.<sup>1</sup> Although not required for voluntary PPIs like TRADENAME, we recommend adding this language to all FDA-approved patient labeling for consistency.

### **Tradename (sumatriptan) Instructions for Use (IFU)**

1. The Applicant’s proposed IFU has the following scores:
- Flesch Reading Ease: 46.2%
  - Flesch-Kincaid Grade Level: 9.1

The sponsor’s readability scores for the IFU are higher than that recommended for optimal patient comprehension. We recommend that the sponsor simplify the IFU by incorporating our recommendations.

Our revised IFU has the following readability scores:

- Flesch Reading Ease: 60.8%
  - Flesch-Kincaid Grade Level: 9.1
2. We recommend adding an illustration labeling all the parts of the Tradename pen.
3. Do not use all capital letters in patient information because they are difficult to read. For better comprehension and to call attention to important information, use other techniques such as bolded font or text boxes.
4. The applicant should provide figures with corresponding text throughout the IFU. The figures should be located either next to or immediately above or below the corresponding text.
5. Recapping can lead to needle stick injury. The Applicant should provide instructions and a figure on how to recap the needle safely. For example “scoop” the cap on.

Please let us know if you have any questions.

9 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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<sup>1</sup> 21 CFR 208.20 (b)(7)(iii)