CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

RISK EVAULATION AND MITIGATION STRATEGY REVIEW

Date:	January 28, 2014
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Subject:	Review to determine if a REMS is necessary
Drug Name(s):	Humalog KwikPen (Insulin lispro 200units/mL)
Therapeutic class & dosage form:	Insulin Subcutaneous injection via Pen
OND Review Division	Division of Metabolism and Endocrinology Products
Application Type/Number:	NDA 205747
Application received	May 10, 2013
PDUFA/Action Date	March 10, 2014
Applicant/sponsor:	Eli Lilly
OSE RCM #:	2013-1191
TSI #:	n/a

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1 INTRODUCTION

This review by the Division of Risk Management evaluates if a Risk Evaluation and Mitigation Strategy (REMS) is needed for the Humalog KwikPen, insulin lispro 200 units/mL. The proposed indication for Humalog KwikPen is to improve glycemic control in adults and children with diabetes mellitus.

Eli Lilly and Company (Lilly) did not propose a REMS for Humalog KwikPen (b) (4)

1.1 BACKGROUND

Lilly submitted an NDA for a U-200 formulation of insulin lispro in a 600 Unit KwikPen. Insulin lispro U-200 is a concentrated form of insulin lispro U-100 (Humalog). Insulin lispro (rDNA origin) is a rapidly acting human insulin analog, parenteral blood glucose-lowering agent.

The KwikPen device is a pre-filled 3mL (b) (4) cartridge pen injector that delivers insulin lispro via subcutaneous injection. The KwikPen mechanism for Humalog 200unit/mL has been designed to allow variable dosing in 1 unit (0.005mL) increments to a maximum dose of 60 units (0.30mL).

1.2 REGULATORY HISTORY

Lilly submitted a supplemental NDA submission to Humalog NDA 020563 on March 15, 2013 for Humalog 200units/mL. In a teleconference with Lilly on 24 April 2013, the Agency informed Lilly that an original NDA would be required for this formulation and device. Therefore, on May 10, 2013, Lilly submitted an original new drug application with references to the Humalog U-100 NDA 020563 for established and documented knowledge about the active pharmaceutical ingredient's safety and efficacy, nonclinical, and quality information. Humalog KwikPen, insulin lispro 200 units/mL, has a proposed indication to improve glycemic control in adults and children with diabetes mellitus. On July 23, 2013, the Agency notified Lilly that the application was sufficiently complete to permit a substantive review. The Prescription Drug User Fee Act (PDUFA) goal action date for the application is March 10, 2014.

The KwikPen device was discussed in a July 22, 2011 Type C meeting. The FDA agreed with the sponsor that the KwikPen is appropriate to use for multiple products under development.

2 MATERIALS REVIEWED

We reviewed the following from the application submitted May 10, 2013:

- Summary of Risk Minimization Activities
- Humalog (b) (4) KwikPen Summative Human Factors Study Technical Report
- Humalog (b) (4) KwikPen Human Factors Engineering and Usability Engineering Report (HFE/UE)
- Clinical Overview
- Proposed draft labeling

Additionally, we reviewed the following:

- September 2013 email information request from the Division of Medication Error Prevention and Analysis (DMEPA) and the sponsor's October 23, 2013 response.
- DMEPA's August 8, 2013 Proprietary Name Review denying the proposed name Humalog (b) (4) KwikPen.
- Institute for Safe Medication Practices (ISMP) October 31, 2013 Medication Safety Alert, "As U-500 insulin safety concerns mount, it's time to rethink use of strengths above U-100." Available at www.ismp.org. Accessed November 22, 2013.

3 RESULTS OF REVIEW

3.1 OVERVIEW OF DEVELOPMENT PROGRAM

Lilly did not submit new clinical data in support of the application; instead, they referenced previous clinical data submitted for Humalog U-100, and they submitted bioequivalence data comparing the bioequivalence of Humalog U-100 and Humalog U-200 insulin.

Lilly submitted the results of a human factors study addressing potential use problems in patients, caregivers, nurses, pharmacists, and prescribers. Using data from various sources,[1] Lilly summarized the known problems with the KwikPen device. Lilly addressed each of the known problems with KwikPens in the development of Humalog 200 units/mL.

3.2 SAFETY CONCERNS

There are a number of known safety issues with the use of the KwikPen and similar devices. Known safety issues[2] with the KwikPens and similar devices and with non-standard insulin concentrations and the sponsor's response to address the issue include:

[1] Databases searched included MAUDE, MDR, ISMP Medication Alerts, CDRH Alerts and Notifications, FDA Enforcement Reports, ECRI Medical Device Safety Reports, and Joint Commission Sentinel Events Alerts

[2] Obtained by the applicant from the safety databases listed in reference 1.

- transmission of blood borne disease when KwikPens are used for multiple patients (sponsor response—packaging now includes notification that the KwikPen is to be used only for a single patient, and that insulin should not be removed from the device with a syringe)
- dispensing of incorrect product, mixing up pens with different medications (sponsor response—distinct visual appearance)
- needlestick injuries (sponsor response—large cap opening allows scooping of needle, IFU instructs to discard used needles)
- jammed or broken pens (sponsor response—IFU contains troubleshooting instructions for possible problems)
- hard-to-read numbers on the dosing dial (sponsor response—dose and pointer touching each other to avoid misreading of dose, instructions that patients with visual impairments should seek assistance or use another product)
- confusion about how to use the pen (sponsor response—IFU with step-by-step instructions)
- cap removal and fit (sponsor response—IFU contains instructions on removing and replacing cap)
- lack of appreciation of risk from using a U-100 syringe to measure non-standard concentrations of insulin (sponsor response—warning label attached to pen , "Do not transfer to a syringe overdose can result")

Using the known problems with KwikPens and similar devices, and known errors with insulin in concentrations other than 100 units per mL, Lilly conducted a human factors study examining the following:

- Normal use of the pen
- Jammed pen requiring troubleshooting
- Prescription writing
- Device dispensing
- Differentiation from other similar products

Patients and caregivers were tested on scenarios requiring them to select the correct product, dialing and administering the correct dose into simulated skin, and troubleshooting a jammed pen. Among the 83 patients and caregivers tested were patients with vision impairment, patients with hand function impairment, and elderly patients. Patients were tested for selecting the correct pen, dialing and injecting the correct dose, and troubleshooting a jammed pen. Healthcare providers tested included 15 nurses, 16 pharmacists, and 16 prescribers. Testing for nurses involved scenarios requiring nurses to select the correct product and administer the correct dose. Testing for pharmacists involved scenarios requiring pharmacists to dispense the correct product with the correct instructions for the patient. Testing for prescribers involved scenarios requiring prescribers to write retail prescriptions and hospital orders transferring patients from U-100 insulin to U-200 insulin, and writing prescriptions for patients being

initiated on U-200 insulin.

Normal pen use among patients, caregivers, and nurses resulted in the following errors:

- five instances (out of 98 tests) of dialing incorrect dose; two of the five had hand or vision impairments
- two instances of not dialing any dose after correctly priming the pen
- one instance of depressing the injection button before inserting the needle; the sponsor assessed this error to be an artifact of the study (patient would be unlikely to do this when actually administering insulin instead of using injection pad)
- nine instances of the dial not returning to zero after completion of injection; the sponsor assessed these errors to an artifact of the study (interaction between pen and injection pad)
- two instances of moving the pen around during the injection; the sponsor assessed these errors to be an artifact of the study (patient would be unlikely to do this when actually administering insulin instead of using injection pad)

Pen differentiation by patients and caregivers resulted in three of 83 instances of selecting the wrong pen, but none of these errors would have resulted in an error in dosing.

Pen differentiation by nurses and pharmacists was conducted without error.

In two of 98 jammed pen scenarios, one patient and one nurse withdrew insulin with a syringe and each made an error in calculating the volume to withdraw.

Regarding the scenarios unique to healthcare providers, there were no errors in product differentiation, or in dispensing and writing a label for the dispensed product. One prescriber wrote an incorrect prescription in the scenario of transferring a patient from U-100 insulin to U-200 insulin, and two prescribers wrote incorrect prescriptions for patients starting on insulin therapy with U-200 insulin. In all three cases (out of 48 total tests), the prescriber incorrectly ordered one-half the needed insulin, each incorrectly dividing the number of units in half when prescribing U-200 insulin. The errors would have resulted in patients receiving less insulin than intended.

3.3 Risk Management Proposed by the Sponsor

The sponsor did not propose a REMS for Humalog 200 units/mL KwikPen. (b) (4) [redacted]

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4 DISCUSSION OF A REMS

The safety issues with KwikPens are similar to other insulin pen delivery devices (e.g., FlexPens), but these safety issues have been manageable with routine measures[3,4]. The safety concern considered for a REMS for this product is the possibility of dosing errors because the insulin is in a concentration other than 100 units/mL.

A patient and a nurse made calculation errors withdrawing insulin from the KwikPen in jammed pen scenarios in human factors testing. The sponsor responded to these errors by strengthening the warning on the KwikPen itself warning against withdrawing the insulin from a jammed pen with a syringe. However, despite the strengthened warning, it is likely that occasionally a user will attempt to remove insulin from a jammed pen; e.g., if the patient needs a dose of insulin and the only insulin available is in the jammed pen. The best solution to this scenario is to engineer the pens so that the pens do not malfunction, or to engineer the pen so that it is not possible to remove the insulin with a syringe.

Three prescribers made errors in prescribing scenarios in human factors testing. In each case, the prescriber erroneously divided the number of units by one-half to adjust for the more concentrated insulin. In each case, the error would have resulted in the patient receiving one-half the dose intended. This error, as it surfaced in the human factors study, would not result in overdose. Theoretically, a prescribing error could be made resulting in too much insulin being prescribed, but it did not occur in the human factors testing conducted, and it seems less likely that prescribers would err by multiplying the dose needed by two to adjust for a more concentrated product.

Insulin 500 units/mL is available in vials, without a corresponding U-500 syringe to measure the insulin. ISMP reported in October 2013 that numerous errors have been reported to ISMP, reportedly due to confusion in drawing up U-500 insulin in U-100 syringes. Because insulin pens eliminate the need to measure insulin, ISMP recommended that insulin other than U-100 insulin be available only in pens to prevent the medication errors resulting from measuring confusion.

5 CONCLUSION/RECOMMENDATION

We believe that labeling, including the Instructions for Use, is sufficient to mitigate the possibility of errors resulting from the introduction into the market of this U-200 insulin. The errors noted in human factors testing would not result in overdose and hypoglycemia, except possibly when insulin is removed with a syringe from a jammed pen. The applicant proposes to place a cautionary label on the barrel of the pen to warn users not to withdraw insulin from the pen with a syringe. We agree with adding a cautionary label as proposed by the applicant. A REMS is unlikely to further mitigate the risk of inappropriate withdrawal of insulin from a jammed pen. Ideally, the pen should be

[3] Routine measures include labeling and pharmacovigilance

[4] Humalog 100 units/mL, Humalog mix 75/25, and Humalog mix 50/50 are all available in the KwikPen.

engineered so that pens do not jam and/or removal of insulin with a syringe is not possible.

Noting the experience with U-500 insulin, ISMP has alerted the medical community that non-standard concentration insulin can cause medication errors due to measuring confusion. For this reason, they recommend that non-standard concentration insulin be available only in pens to avoid measuring confusion. There might be a need for a broader FDA safety initiative regarding the overall issue of non-standard concentration insulin. However, we do not believe that a product-specific REMS would be helpful in dealing with the larger safety issue.

We ask that DMEP include DRISK in future discussions regarding this issue.

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/s/

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