

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201739Orig1s000

**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**

DRISK REMS REVIEW

Date: March 21, 2011

To: Badrul Chowdhury, MD, Director
Review Division of Pulmonary, Allergy, and
Rheumatology Products (DPARP)

Through: Claudia Karwoski, Pharm.D., Director
Division of Risk Management (DRISK)

From: **Scientific Lead**, Risk Management Analyst (RMA)
Reema Jain, Pharm.D., M.P.H., DRISK

Team Leader, Kendra Worthy, Pharm.D., DRISK

DRISK Review Team: Mary Dempsey, Risk Management Program Coordinator
Twanda Scales, RN, MSN/Ed, Patient Labeling Reviewer

Subject: Review of Sponsor Proposed Risk Management Plan
submitted September 29, 2010

Drug Name (Established Name): Epinephrine Auto-Injector

Application Type/Number: NDA 201-739

Applicant: Intelliject Inc.

OSE RCM #: 2010-2319

1. INTRODUCTION

This review follows a request from the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) for the Office of Surveillance and Epidemiology (OSE), Division of Risk Management (DRISK) to review Intelliject Inc.'s September 29, 2010 submission for an Epinephrine Auto-injector (EAI)¹ containing a proposed risk management plan.

2. MATERIALS REVIEWED

The following materials were reviewed by DRISK for comment in this interim review:

- Intelliject proposed Risk Management Plan Overview for Epinephrine Auto-Injector, received September 29, 2010
- Intelliject proposed Detailed Risk Management Plan for Epinephrine Auto-Injector, received September 29, 2010
- Intelliject proposed Risk Management Plan Appendices for Epinephrine Auto-Injector, received September 29, 2010

The following materials were referenced in this interim review:

Prescribing information

- Intelliject proposed Prescribing Information for Epinephrine Auto-Injector, received September 29, 2010

Sponsor Submissions

- Intelliject Clinical Overview for Epinephrine Auto-Injector, received January 27, 2011

3. BACKGROUND

Intelliject, Inc. (Intelliject) developed an Epinephrine Auto-Injector 0.15 mg (epinephrine injection USP 1:1000) and Epinephrine Auto-Injector 0.3 mg (epinephrine injection USP 1:1000), collectively referred to as EAI, or individually referred to as EAI 0.15 mg and EAI 0.3 mg. EAI is a compact, patient-actuated, auto-injection system that delivers epinephrine injection, USP 1:1000 (or 1 mg/mL) as a single dose of either 0.3 mg (0.3 mL) for patients \geq 30 kg or 0.15 mg (0.15 mL) for patients 15-30 kg intramuscularly or subcutaneously. The proposed indication for EAI is for the emergency treatment of allergic reactions (Type I), including anaphylaxis. The sponsor submitted the application on September 29, 2010 as a 505(b)(2) submission, using the FDA approved EpiPen[®]/EpiPen Jr[®] (NDA 019-430) as the reference listed drug (RLD).

EAI utilizes a device as the drug delivery system to inject the epinephrine. The device component of EAI is a gas powered, needle-based system that delivers the prescribed dose of epinephrine into the user once activated. The needle is fully and automatically retracted within the housing of the device following use. The EAI also includes an electronic prompt system that

¹ During development, the product has been referred to as [REDACTED] (b)(4). However, the brand name is currently under CDER review; therefore, the product is referred to as EAI throughout this document.

provides audible and visual cues to guide a user through the injection process. This electronic prompt system works independently from the mechanical functionality of the epinephrine delivery system in the device. Furthermore, the device is self-contained and requires no assembly, priming, or attachments by the patient or caregiver.

4. RESULTS OF REVIEW

4.1. Sponsor's Submission

EAI was examined in one pivotal clinical study (INT0802) that was a Phase I comparative clinical bioavailability/bioequivalency study in 69 healthy volunteers (age 23-45 years) using EAI 0.3 mg. The study was a randomized, active controlled, 3-sequence, 3-period, cross-over study in which subjects were administered a single injection of the EpiPen (RLD) for 2 periods and EAI for 1 period. Among the 69 volunteers, there were no deaths, serious adverse events (SAEs), or otherwise significant adverse events (AEs). Among the treatment emergent AEs (TEAEs), 87% occurred after the administration of the RLD and 69% occurred after the administration of EAI. Of the TEAEs reported with EAI, 98% were classified as mild; the remaining cases were classified as moderate and included 1 case of tachycardia and 1 case of injection site pain. The preferred terms that occurred in at least 2 subjects and at a higher rate after EAI administration as compared to RLD administration included tachycardia (17.9% and 17.8%, respectively) and anxiety (10.4% and 7.4% respectively). The most commonly reported TEAEs for EAI were injection site erythema (31% vs 33% for EpiPen), heart rate increased (18% vs 18% for EpiPen), tremor (13% vs 14% for EpiPen), and injection site pain (10% vs 24% for EpiPen).

In addition to the pivotal study, Intelliject completed three human factors simulated clinical use studies (INT0801, INT-FE-0901, and INT0803). The objective of these studies was to evaluate device- and human factors-related aspects of the auto-injector. The studies validated the clinical use and effectiveness of the device by simulating use of EIA using sham or actual devices. The results of these 3 studies provide qualitative support for the usability of the device and identified zero device failures among 505 tested devices.

4.2. Sponsor's Proposed Risk Management Plan

The sponsor's risk management plan addresses the risks related to the administration of epinephrine via the device component of the EAI. The sponsor proposed the following minimization measures:

- A mechanism enabling patients to practice use of the device with a Trainer device that contains no active ingredient but allows the patient to practice using under non-emergency conditions
- Clear differentiation between the 2 dosage strengths using different color labeling (orange for 0.3 mg and blue for 0.15 mg)
- An electronic prompt system built into both the Trainer device and EAI device that includes both visual and audible cues for the patient
- Written patient information leaflet with instructions and visual diagrams depicting appropriate administration

- Routine pharmacovigilance of the safety profile

5. DISCUSSION

Currently, there are 3 approved epinephrine auto-injector brand names, EpiPen[®]/EpiPen Jr[®] (NDA 019-430), Twinject[®] (NDA 020-800), and Adrenaclick[®] (NDA 020-800). EpiPen/EpiPen Jr was used as the RLD for the EAI 505(b)(2) application submitted on September 29, 2010.

EAI contains epinephrine, which is a sympathomimetic. Epinephrine can increase heart rate, increase vasoconstriction, and increase bronchial smooth muscle relaxation via the alpha and beta adrenergic receptors. The safety profile for EAI demonstrated in the pivotal trial (INT0802) is not unique to EAI. The majority of the adverse events (98%) in the trial were mild in severity and all events resolved; the most commonly reported TEAEs for EAI were injection site erythema (31%), heart rate increased (18%), tremor (13%), and injection site pain (10%). The frequency of these most commonly reported TEAEs for EpiPen was comparable or higher than EAI in the trial. The adverse drug reactions identified in the study can be adequately communicated through the labeling for EAI.

The risks identified by the sponsor in the proposed risk management plan for EAI are related to the design of the drug delivery system: (1) usability, and (2) differentiation between the 2 doses. The sponsor included several mechanisms built into the device's technology to address these risks.

6. CONCLUSION

DRISK believes that the proposed approach by the sponsor is adequate at this time. Additional risk mitigation strategies such as a Medication Guide, communication plan, and/or Elements to Assure Safe Use do not appear to be warranted. The safety profile for epinephrine is well established and the safety profile for EAI is consistent with the currently approved epinephrine auto-injectors (e.g., EpiPen, Twinject, and Adrenaclick). There were no new or unique safety concerns associated with EAI in the pivotal trials. Furthermore, none of the currently approved epinephrine auto-injectors have an approved risk evaluation and mitigation strategy (REMS).

Should DPARP raise further concerns with the risks outlined above or identify additional risks associated with EAI warranting more extensive risk mitigation or a formal REMS, please send a consult to OSE DRISK.

This memo serves to close the existing consult request for EAI under NDA 201-739, epinephrine auto-injector. Please notify DRISK if you have any questions.

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

/s/

REEMA JAIN
03/21/2011

CLAUDIA B KARWOSKI
03/21/2011
concur