

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
206538Orig1s000

**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
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategy (REMS) Review

Date: January 28, 2015

Reviewer(s): Amarilys Vega, M.D., M.P.H, Medical Officer
Division of Risk Management (DRISK)

Team Leader: Naomi Redd, Pharm.D, Acting Team Leader
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Division Director: Cynthia LaCivita, Pharm.D, Acting Director
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Drug Name(s): Insulin glargine [rDNA origin] (Toujeo SoloStar)

Therapeutic Class: Antidiabetic agent

Dosage and Route: 300 Units/mL, injection

Application Type/Number: NDA 206538

Submission Number: ORIG-1, April 25, 2014

Applicant/sponsor: Sanofi-Aventis U.S. LLC.

OSE RCM #: 2014-865and 2014-866

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that should not be released to the public.**

1 INTRODUCTION

This review documents the Division of Risk Management's (DRISK) evaluation of whether a Risk Evaluation and Mitigation Strategy (REMS) is necessary for Insulin glargine [rDNA origin, HOE901-U300] (NDA 206538, Toujeo SoloStar). Sanofi-Aventis U.S. LLC is seeking approval for HOE901-U300 to improve glycemic control in adults with diabetes mellitus. Insulin glargine injection, 300 Units/mL will be available in a 1.5 mL glass cartridge assembled in a disposable pen injector.

Sanofi-Aventis did not submit a Risk Evaluation and Mitigation Strategy (REMS) but proposed several voluntary risk mitigation measures with this application.

1.1 BACKGROUND

Diabetes affects a large percentage (8.3%) of the United States population.¹ Diabetes mellitus (Types 1 and 2) is a chronic disease that, when uncontrolled, is associated with chronic microvascular and macrovascular complications which can result in retinopathy, nephropathy, neuropathy and premature cardiovascular morbidity and mortality.

There are numerous treatment alternatives for diabetes mellitus (e.g., biguanides, sulfonylureas, GLP-1 agonists, DPP-4 inhibitors, insulin analogs, SGLP-2 inhibitors). However, many diabetic patients still have suboptimal glycemic control on currently available medications. There is a need for an antidiabetic product that will provide a constant insulin supply over 24 hours but with a low risk of hypoglycemia.

Insulin glargine is approved and marketed in the U.S. since April 20, 2000 as Lantus[®] (insulin glargine [rDNA origin] injection, 100 Units/mL) for once daily subcutaneous injection to improve glycemic control in adults and pediatric patients with type 1 and 2 diabetes mellitus. Hypoglycemia is the most common adverse reaction of insulin, including Lantus. The risks associated with Lantus are communicated through labeling only.

HOE901-U300 is a new formulation of insulin glargine which showed a flatter and prolonged (up to 36 hours) profile of the insulin concentration and glucose-lowering activity when compared with Lantus at matching doses.

1.2 REGULATORY HISTORY

Following is the regulatory history, in pertinent part.

- **April 20, 2000:** Insulin glargine registered and marketed in the U.S. as Lantus[®] (insulin glargine [rDNA origin] injection, 100 Units/mL) for once daily subcutaneous administration to improve glycemic control in adults and pediatric patients with type 1 and 2 diabetes mellitus.
- **April 25, 2014:** HOE901-U300 application received by FDA.
- **July 7, 2014:** FDA approves tradename, Toujeo SoloStar.

¹ Centers for Disease Control and Prevention, data available as of 2010, accessed at: <http://www.cdc.gov/diabetes/consumer/research.htm>, September 22, 2014.

- **September 22, 2014:** Mid-cycle meeting. (b) (4)
[REDACTED]
[REDACTED] No significant safety concerns identified. A human factors study demonstrated that prescribers were able to understand the specifics about the dosing and administration of HOE901-U300 with the information provided in the label.

Important upcoming dates:

- **February 25, 2015:** PDUFA date

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

- Introduction, dated April 1, 2014
- Clinical Overview, dated March 24, 2014
- Justification for not submitting a REMS, April 25, 2014
- Draft Insulin glargine 300 u/mL label, April 25, 2014
- Sarah K. Vee, Pharm.D., Division of Medication Error Prevention and Analysis Review, November 3, 2014

3 RESULTS OF REVIEW

At the time this review was completed, FDA's review of the dossier submitted by the Applicant in support of the efficacy and safety of HOE901-U300 was still ongoing.

3.1 OVERVIEW OF CLINICAL PROGRAM²

Insulin glargine is the same active substance in Lantus and HOE901-U300; therefore, the application cross-referenced to the nonclinical summaries and study reports and CMC drug substance information submitted to the Lantus NDA 021081.

The evaluation of the efficacy and safety for HOE901-U300 was based on thirteen studies: six Phase 1 studies (PKD10086, PKD11627, PKD12270, PKD13560, PDY12335, and TDR11626), one Phase 2 study (PDY12777), four pivotal Phase 3 studies (EFC11628, EFC11629 and EFC12347 in T2DM, EFC12456 in T1DM) and two 3-month sub-studies embedded in studies EFC11628 and EFC11629 to compare the efficacy and safety of HOE901-U300 when injected up to 3 hours earlier or later than the patient's usual once daily basal insulin injection time. A total of 1,686 patients received at least one dose of HOE901-U300.

Non-inferiority of HOE901-U300 versus Lantus was demonstrated consistently in all four pivotal Phase 3 studies.

Regarding safety, the total number of deaths was balanced between the two groups and no new safety concerns were identified for HOE901-U300.

² Clinical Overview, dated April 25, 2014 and mid-cycle clinical

The Division of Medication Error Prevention and Analysis (DMEPA) evaluated a Human Factors Study included in this application. DMEPA determined that users were able to use the prefilled pen safely and effectively with no reported instance of calculation errors. However, errors in dosing may occur given that HOE901-U300 contains a new concentration of insulin. Therefore, DMEPA determined that proper education and training provided prior to the first injection is required to ensure the safe use of the product. DMEPA recommended revisions to the physician insert, pen label and carton labeling to prevent misuse of the product.

3.2 RISK MITIGATION ACTIVITIES PROPOSED BY THE SPONSOR

The sponsor considered that a REMS is not required for this application. The sponsor determined that the risks associated with Lantus (hypoglycemia, hypersensitivity reactions, medication errors) are also applicable to HOE901-U300 and proposed labeling, routine pharmacovigilance, and several voluntary risk mitigation measures outside of a REMS.

The proposed labeling includes a Patient Package Insert and Instructions for Use. Voluntary risk mitigation measures focus on the correct use of the product and include the following:

- Dear Healthcare Provider Letter
- Guide for Healthcare Professionals
- Patient Brochure
- Letter to Professional Organizations
- Additional educational materials: publications, speaker programs, web-based programs and other information delivered via multiple types of media at the point of care and the local environment

4 DISCUSSION

The clinical development program demonstrated the efficacy and safety of HOE901-U300 to improve glycemic control in adults with diabetes mellitus. The safety profile of HOE901-U300 is consistent with that of Lantus including the serious risks of hypoglycemia. Hypoglycemia is a well-known complication of antidiabetic agents. The anticipated prescriber populations (endocrinologists, internists, and family practitioners) are familiar with the management of patients with diabetes and the risk of hypoglycemia associated to this disease. The risk of hypoglycemia associated to the use of Lantus has been effectively communicated through labeling.

DMEPA determined that based on the Human Factor studies, measures beyond labeling are not required to ensure that prescribers and patients are able to use HOE901-U300 safely. Additional risk management activities proposed by the sponsor focus on the appropriate use of HOE901-U300. DRISK does not advise against the sponsor implementing these additional, voluntary risk management activities. These additional risk management activities are not necessary to ensure the benefits outweigh the risk of the drug.

5 CONCLUSIONS AND RECOMMENDATIONS

DRISK determined that a REMS is not required to manage the risks associated to HOE901-U300. DRISK concurs with the Division of Metabolism and Endocrinology Products' (DMEP) recommendation to communicate the serious risks of hypoglycemia associated to HOE901-U300 through labeling. The risks for hypoglycemia will be included in the Warnings and Precautions section of the label.

If new safety concerns emerge during the review of this application, please include DRISK in any discussion regarding selection of a risk management approach.

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/s/

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